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REVIEW ARTICLE

No new needle in the COVID-19 therapeutic haystack: A COVID-19 therapeutics analysis

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Abstract

Despite nearly 5000 United States Food and Drug Administration (FDA)-tracked trials, no new FDA- or European Union-approved Coronavirus Disease 2019 (COVID-19) drug was discovered during the COVID-19 pandemic. Fortunately, drugs developed before the pandemic proved highly effective, particularly when used early in vaccinated patients. The most powerful treatments are antivirals targeting the spike structural protein and two non-structural proteins (NSPs), NSP5 (main protease [Mpro]) and NSP12 (RNA-directed RNA polymerase [RdRp]). Notably, two studies published before the pandemic and one shortly after its declaration had already identified these three key targets. New monoclonal antibodies were designed to block the spike protein from binding to the host cell. However, all such antibodies were eventually rendered ineffective by emerging viral variants. Several drugs previously used for Middle East respiratory syndrome, Ebola, respiratory syncytial virus, and other viruses work by disrupting the replication activity of Mpro and RdRp. Convalescent plasma, a treatment used since 1900, showed mixed results. For hyperinflammation, only three rheumatoid arthritis drugs and one glucocorticoid, also used in arthritis treatment, received approval. No new approaches were developed to treat blood clots or improve oxygenation. Despite a wartime-like focus and unprecedented research intensity, no respiratory illness, including COVID-19, has yet been cured. Using a personal database of 3050 therapeutic research papers, along with data from ClinicalTrials.gov and Google Scholar, this review examines approved, promising, and ineffective COVID-19 therapeutics. Potential candidates currently undergoing clinical trials are identified to highlight future therapeutic possibilities and guide ongoing research efforts.

Keywords: COVID-19; Therapeutics; Antivirals; Hyperinflammation

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1. Introduction

Although nearly 5000 clinical trials were tracked by the United States (US) Food and Drug Administration (FDA), no new FDA- or European Union (EU)-approved Coronavirus Disease 2019 (COVID-19) drug was developed during the COVID-19 pandemic. However, drugs developed before the pandemic proved highly effective, despite the eventual loss of efficacy of monoclonal antibodies due to emerging viral variants. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, affects all major organs through several mechanisms, as summarized in Table 1.

The seemingly simple question – "What will happen if I get COVID-19 and follow a treatment regimen?" – is impossible to answer definitively. The complex interplay of viral variants, vaccination history, comorbidities, prior infection, and available therapeutics creates enormous possible outcomes. However, the recommended therapeutic approach is relatively clear. Following vaccination, the first step is to reduce viral replication through the prompt use of antivirals – currently, Paxlovid is the best option for those eligible to take it. If the virus has already replicated explosively, subsequent therapeutic interventions to mitigate COVID-19 impacts are also fairly well established.

Therapeutics for COVID-19 is a technically complex field, involving discussions of the virus (SARS-CoV-2), the disease (COVID-19), therapeutic strategies, the immune system, and aspects of cellular biology.

Since the beginning of the pandemic, I have been summarizing COVID-19 research papers in a document titled "The Mouse That Roared" (R. L. Martin, unpublished report, 2025) – so named because SARS-CoV-2, a relatively mild virus, has caused profound societal impacts. The document spans approximately 21,000 pages and includes summaries of around 17,000 papers drawn from 2,250 sources. Each journal within a journal family was counted separately, e.g., 140 BMC journals were included. Most therapeutic papers were published in *Nature*, *Cell*, *Science*, *MDPI*, *Cureus*, *Journal of the American Medical Association*, *British Medical Journal*, *New England Journal of Medicine*, and *Proceedings of the National Academy of Sciences*, as well as other journals from Wiley Whiley, BMC, PLOS, the American Health Association, Sage, Frontiers, bioRxiv, medRxiv, preprints.org, SSRN, Research Square, and the Centers for Disease Control and Prevention (CDC). The document is organized into 32 chapters and nine appendices covering diverse topics, e.g., "Historical Perspective," "SARS-CoV-2," "COVID Disease Progression," "How People Behave," "Economics," "Vaccine Effectiveness," "Second Generation Vaccines," "Political and National COVID Responses," and "Preparing for the Next Pandemic." The "Therapeutics" chapter is the basis for this review.

2. Treatment/therapeutic strategy

The treatment/therapeutic strategy is summarized in the second bar beneath the disease progression diagram in Figure 1.

Therapeutic actions corresponding to the four treatment/therapeutic phases illustrated in Figure 1 are summarized in Table 2.

It is discouraging to note that:

(i) Many diseases, especially those that are rare, genetic, or complex, still lack definitive cures

(ii) No respiratory disease has ever been cured.

The US National Institute of Health (NIH) produced 72 versions of highly comprehensive COVID-19 treatment guidelines. These documents expanded from 90 pages to 278 pages within 12 months, eventually reaching 478 pages. The final version of the NIH COVID-19 treatment guidelines was released on February 29, 2024.

3. Therapeutic surge

During the pandemic, pharmaceutical companies and academic researchers pursued new therapeutics with World War II-like urgency and focus. Several websites tracked global therapeutic trials:

- No longer operational, the Global Coronavirus COVID-19 Clinical Trial Tracker listed 2533 trials as of December 31, 2020
- No longer being updated, the World Health Organization Treatment Tracker listed 4634 trials as of August 2023
- ClinicalTrials.gov (https://clinicaltrials.gov/) is still operational.

A 2021 study reported that many trials investigated the same drugs, but most were too small in sample size to draw definitive conclusions.[1] As will be shown, some of the therapeutics discussed in this review are supported by numerous studies, yet the results are often contradictory.

Table 1. Mechanisms of SARS-CoV-2 damage infection in major organs/systems

Organ/system	Direct viral damage	Hyperinflammation	Blood clots	Lack of oxygen	Other
Heart	✓	✓	✓	✓	Stress
Lungs	✓	✓	✓	✓	Scarring
Kidneys	✓	✓	✓	✓	Microvascular damage
Liver	✓	✓	✓	✓	COVID-19 drug injury
Pancreas	✓	✓	✓	✓	Increased triglycerides, reduced blood flow
Nervous system	✓	✓	✓	✓	Metabolic dysfunction

Abbreviation: SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

For example, the Phase 3 trial for the Pfizer mRNA vaccine included 43,448 participants, whereas the initial Phase 3 trial for Paxlovid enrolled 2246 adult participants. A 2024 study summarized global COVID-19 clinical trials through April 23, 2023,[2] as shown in Figure 2.

Table 2. Treatment/therapeutic phases

Treatment/ therapeutic phase	Damage being addressed			
	Direct viral damage	Hyperinflammation	Blood clots	Lack of oxygen
Prevent infection	✓			
Suppress viral replication and inflammation	✓	✓	✓	
Suppress hyperinflammation		✓	✓	✓
Suppress organ damage			✓	✓

Table 3 summarizes data from ClinicalTrials.gov and therapeutic paper statistics from "The Mouse That Roared" (R. L. Martin, unpublished report, 2025), as of November 01, 2024. 1686 COVID-19 vaccine trials are excluded from this summary.

For perspective, there were 1107 FDA clinical trials for triple-negative breast cancer, 720 for the flu, 193 for RSV, and 18 for Addison's disease.

For high-impact therapeutics, Google Scholar was used to identify the paper with the most citations and/or perceived impact. However, this introduces a sample bias, as papers published in prestigious journals or those that are older tend to accumulate more citations. For example, among the 20 therapeutics referenced in this article, the most-cited papers for eight of them were published in the *New England Journal of Medicine*. Furthermore, many of the early, highly cited papers merely suggested that a therapy, such as probiotics, should be investigated or reported in preliminary trials with very small sample

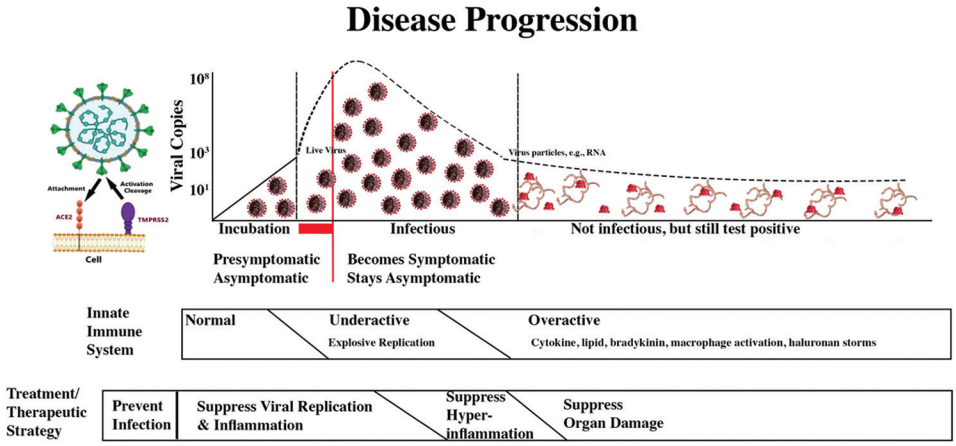
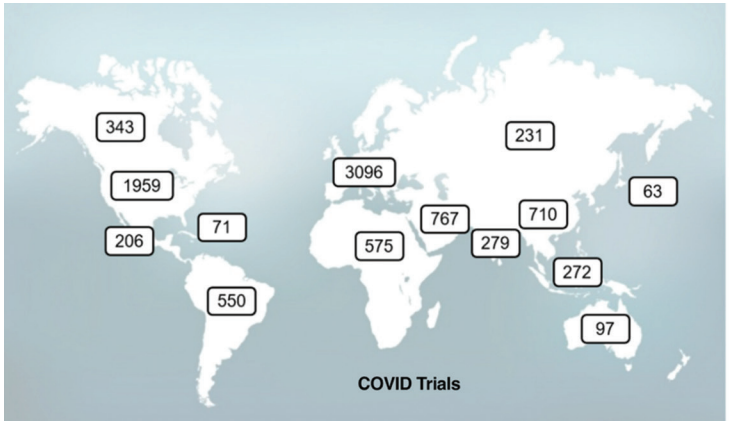


Figure 1. COVID-19 disease progression and treatment/therapeutic strategy. The image was created by the author using Photoshop. Abbreviations: ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane serine protease 2.



Region Name	Number of Studies
World	8,943
Africa	575
Central America	71
East Asia	710
Japan	63
Europe	3,096
Middle East	767
North America	2,399
Canada	343
Mexico	206
United States	1,959
North Asia	231
Pacifica	97
South America	550
South Asia	279
Southeast Asia	272

Figure 2. Global COVID-19 clinical trials as of April 23, 2023. Adapted from Meiraa *et al.*[2]

sizes. These papers are not strong indicators of therapeutic effectiveness.

Highly cited papers with actual therapeutic results were highlighted for two main reasons:

(i) They provide historical perspectives on the development of the therapeutic

(ii) Later papers often contributed little additional insight into the therapeutic impacts.

A therapeutic typically progresses through three trial phases and a regulatory review: Phase 1, which evaluates safety with a small group; Phase 2, assesses effectiveness in a larger group; Phase 3, confirms effectiveness and monitors adverse reactions in a large population.

Clinical trial costs and failure rates represent significant barriers to drug development. Cost estimates are presented in Figure 3, based on a 2014 report from the Office of the Assistant Secretary for Planning and Evaluation.[3] The report indicated that the likelihood of a drug successfully progressing through all phases of clinical trials and obtaining regulatory approval was only 12%.

Cost, success rates, and therapeutic differential advantage are key factors contributing to the low number of therapeutics approved by the FDA each year, as shown in Figure 4.

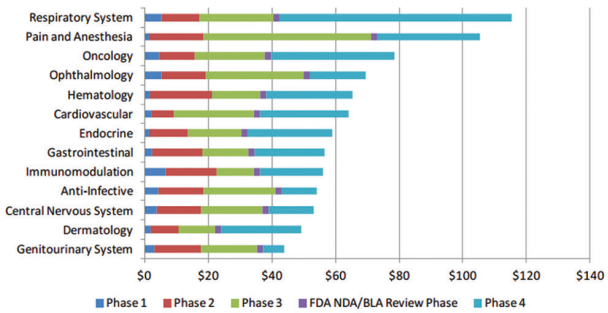


Figure 3. Clinical trial costs (in $ millions) in 2012. Reprinted from Sertkaya *et al.*[3]

An example of a drug that has not reached the market – potentially due to a "good enough" alternative, Paxlovid, is already available – is masitinib. A 2021 paper reported that masitinib (a main protease [Mpro] inhibitor) reduced SARS-CoV-2 viral load by more than 99% and lowered inflammatory cytokine levels in mice.[4] Since early 2023, the sponsoring pharmaceutical company has been attempting to recruit participants for a clinical trial.

4. Testing and targets

There are numerous potential COVID-19 therapeutic targets, including viral proteins, cytokines, immune system cells, and affected organs. Among these, viral proteins are excellent targets for COVID-19 therapeutic intervention. Antivirals, anti-inflammatory agents, and specialized therapeutics have been used as key strategies against these targets, as shown in Table 4.

4.1. "Squeakinstein"

Therapeutic testing typically begins with animal models. While COVID-19 has been reported in wild mice, their angiotensin-converting enzyme 2 (ACE2) receptors are not well-suited for binding SARS-CoV-2. In 2000,

Table 3. Statistics on global COVID-19 clinical trials data and therapeutic papers

ClinicalTrials.gov				Google Scholar	"The Mouse That Roared"
Total	Completed	Terminated	Results		
4855	2222	427	528	~3,000,000[a]	3065

Notes: [a]Google Scholar reported 5,500,000 papers for COVID-19. COVID-19 scholars reported 143,711, the NIH 374,733, and PubMed 53,165. Data from ClinicalTrials.gov, Google Scholar, and "The Mouse That Roared" (R. L. Martin, unpublished report, 2025), as of November 01, 2024.

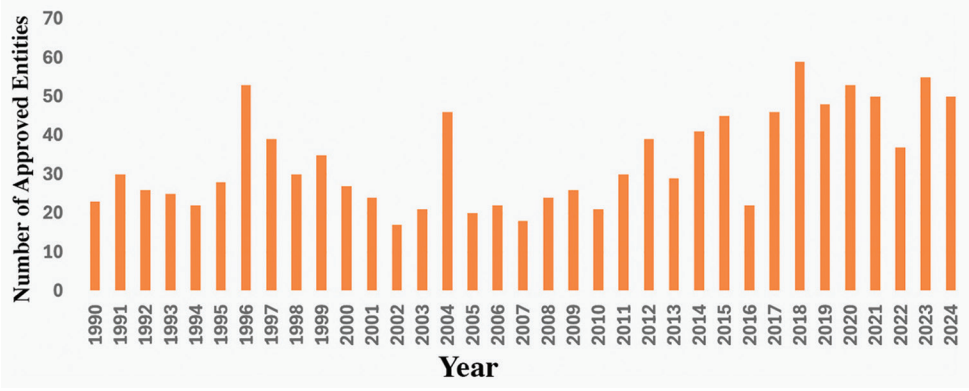


Figure 4. The United States Food and Drug Administration (FDA)-approved new molecular entities by year (new molecular entity vaccines and gene therapies are not included). The image was created by the author using Photoshop based on FDA data.

mice were genetically engineered to express human-like ACE2 receptors – hence "squeakinstein." More recently, advancements in genetic engineering have further refined these models – even enabling the development of mice suited for studying long COVID. A wide range of therapeutics has been tested on these genetically modified mice. In one example, researchers subjected mice to 3 months of swim training to evaluate how exercise might influence immune response.

Table 4. Therapeutic strategies targeting SARS-CoV-2 proteins

Proteins	Antivirals	Anti-inflammatory agents	Specialized therapeutics
Structural proteins			
S	✓	✓	
N	✓	✓	Heart, amyloidosis
M	✓	✓	
E	✓	✓	Kidney, lung
Non-structural proteins (NSP)			
NSP1	✓	✓	
NSP2			
NSP3 (PLpro)	✓		
NSP5 (Mpro)	✓	✓	
NSP6		✓	mRNA transport
NSP7	✓		
NSP8	✓		
NSP9	✓	✓	
NSP10	✓	✓	
NSP11			
NSP12 (RdRp)	✓		
NSP13	✓		
NSP14 (Exon)	✓	✓	
NSP15	✓	✓	
NSP16	✓	✓	
Accessory proteins			
ORF3a	✓	✓	Mitochondrial function
ORF3b		✓	
ORF3c			
ORF6		✓	
ORF7a	✓		
ORF7b	✓		
ORF8		✓	Cholesterol formation
ORF9b			
ORF9c			Mitochondrial function, heart cells, and cholesterol formation
ORF10		✓	

Abbreviations: Mpro: Main protease; PLpro: Papain-like protease; RdRP: RNA-dependent RNA polymerase; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

4.2. Article review in "The Mouse That Roared"

Figure 5 shows the distribution of all COVID-19 therapeutics papers covered in "The Mouse That Roared" (R. L. Martin, unpublished report, 2025) and highlights how many of them received FDA approval. Notably, 75% of the articles focused on antivirals.

5. Infection prevention

Infection prevention (prevent infection phase in Figure 1) article statistics from ClinicalTrials.gov, Google Scholar, and "The Mouse That Roared" (R. L. Martin, unpublished report, 2025) are presented in Table 5. In the table and subsequent similar tables, "Approved" refers to therapeutics that were approved at any point; some approvals were later withdrawn due to reduced effectiveness against emerging variants.

5.1. Approved therapeutics

The only currently FDA-approved COVID-19 therapeutic is Pemgarda. The company that manufactures Pemgarda reported the following Phase 3 trial results:

- An 84% relative reduction in infection risk through month 6
- A 64% reduction in the risk of symptomatic COVID-19 during months 7 – 12 in an immunocompetent adult population.

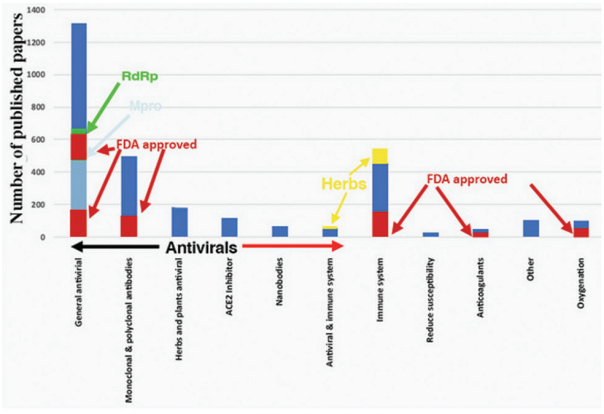


Figure 5. Distribution of COVID-19 therapeutic papers covered in "The Mouse That Roared" (R. L. Martin, unpublished report, 2025)
Abbreviations: ACE2: Angiotensin-converting enzyme 2; Mpro: Main protease; RdRP: RNA-dependent RNA polymerase.

Table 5. COVID-19 infection prevention therapeutics

Category	ClinicalTrials.gov			Google Scholar	"The Mouse That Roared"
	Total	Completed	Results		
Infection prevention[a]	326	145	53	-	-
Approved therapeutics					
Pemgarda	1	0	0	38	1
Promising therapeutics					
Nasal sprays	53	35	4	23,200	78
Probiotics	22	12	2	51,800	7
Limited-effectiveness therapeutics					
BCG vaccination	9	5	0	31,000	26
Vitamin D	89	52	4	1,370,000	49

Notes: [a]Some drugs here are also in treatment categories. Data from ClinicalTrials.gov, Google Scholar, and "The Mouse That Roared" (R. L. Martin, unpublished report, 2025), as of November 1, 2024. Abbreviation: BCG: Bacille Calmette-Guérin.

However, a 2024 bioRxiv preprint reported that viral variants KP.3.1.1 and XEC significantly impacted Pemgarda's neutralization rates.[5] These findings were later confirmed in subsequent articles.

5.2. Promising therapeutics

5.2.1. Nasal sprays

Since intramuscular COVID-19 vaccines offer limited protection in the upper respiratory tract, nasal sprays and gargles have been proposed as complementary therapeutic options. Notably, a nasal spray containing engineered llama nanobodies was shown to protect or even fully cure SARS-CoV-2-infected mice.

(a) Nasal spray or gargle containing 0.5 – 1% povidone-iodine

Several pre-pandemic studies reported that iodine-based nasal spray or gargle effectively eliminated viruses in the nose or mouth. A 2020 paper reported that all evaluated concentrations of nasal and oral antiseptics completely inactivated SARS-CoV-2 within 60 s.[6] A subsequent article from the same journal published in 2022 reported that povidone-iodine nasal spray resulted in an 8.57 times reduction in COVID-19 hospitalization or death rates.[7] Despite these findings, the NIH COVID-19 Treatment Guidelines remain silent on the use of nasal sprays.

5.2.2. Probiotics

A 2020 medRxiv preprint reported that, in an analysis of 327,720 United Kingdom participants, certain dietary supplements were associated with a reduced risk of SARS-CoV-2 infection.[8] Specifically, probiotics were linked to a 14% reduction in infection risk (95% confidence interval [CI]: 8 – 19%). Notably, "The Mouse That Roared" (R. L. Martin, unpublished report, 2025) did not include any articles reporting negative results for probiotics. Despite this, the NIH COVID-19 Treatment Guidelines do not mention probiotics.

5.3. Limited-effectiveness therapeutics

5.3.1. Bacille Calmette-Guérin (BCG) vaccination

The BCG vaccine, developed over 80 years ago for tuberculosis, is one of the most widely used vaccines globally. A 2020 paper proposed that BCG may stimulate "trained immunity" against respiratory infections.[9]

Early in the pandemic, African countries with extensive BCG vaccination had 65% of the COVID-19 case rates compared to neighboring countries with lower BCG vaccination coverage. However, a 2022 paper reported that these differences diminished over time and typically lost statistical significance.[10] Although a few subsequent studies noted minor protective effects, most found no significant benefit. The NIH COVID-19 Treatment Guidelines do not address BCD vaccination.

5.3.2. Vitamin D

Researchers assessed the preventive effects of Vitamins A, C, D, and K against COVID-19, with the majority of studies focusing on Vitamin D. Findings on its effectiveness varied widely. The NIH COVID-19 Treatment Guidelines concluded that there was insufficient evidence to recommend for or against the use of Vitamins C or D for the prevention of COVID-19.

6. Suppression of viral replication and inflammation

The key takeaway from this review is that infection prevention remains the highest priority. Once infected, therapeutics can help but generally have limited effectiveness (suppress viral replication and the inflammation phase in Figure 1). Figure 6 illustrates that promising antiviral targets were identified early in the pandemic.[11]

Table 6 summarizes antiviral article statistics from ClinicalTrials.gov, Google Scholar, and "The Mouse That Roared" (R. L. Martin, unpublished report, 2025). The table highlights therapeutics that receive detailed discussion in this review. As will become evident, nearly all antivirals target either the spike protein or two non-structural proteins – NSP5 (also known as Mpro or $3CL^{pro}$) and NSP12 (also known as RNA-directed RNA polymerase [RdRp]). Even though other structural proteins (e.g., nucleocapsid) and non-structural proteins (e.g., NSP1) represent viable

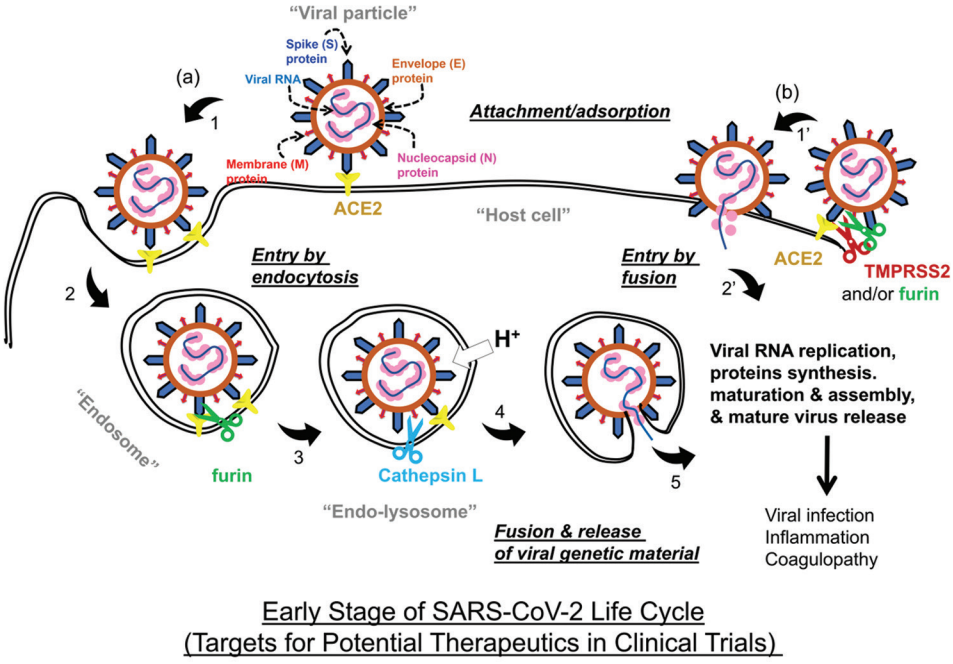


Figure 6. Early viral lifecycle and antiviral targets. Reprinted from Al-Horani *et al.*[11]
Abbreviations: ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane serine protease 2.

antiviral targets, few studies have investigated them, and no approved therapeutics have emerged targeting these proteins.

The three antiviral targets of approved COVID-19 drugs – spike proteins, NSP5 and NSP12 – were discovered early in 2020:

(i) A 2020 *Nature* paper[12] investigated drugs effective against other viruses, e.g., SARS-CoV-1, Middle East respiratory syndrome (MERS)-related coronavirus, and Ebola virus, and reported that remdesivir was likely to be effective against SARS-CoV-2
(ii) A 2020 *Science* paper[13] reported the development of an Mpro inhibitor
(iii) A 2020 *Nature* paper[14] identified the spike protein as an ideal target for vaccines and therapeutics.

6.1. Approved therapeutics

6.1.1. Monoclonal antibodies and nanobodies

Monoclonal antibodies and nanobodies bind to various targets, e.g., cancer cells or viral proteins, causing conformational changes. In the case of SARS-CoV-2, they bind to the spike protein, preventing it from attaching to the ACE2 receptor and entering host cells.

The FDA approved its first monoclonal antibody in 1986 for the prevention of kidney transplant rejection. According to a 2022 study,[15] 162 monoclonal antibodies had been approved worldwide as of June 30, 2022.

Monoclonal antibodies have been developed for a wide range of conditions, including transplants, cancers, sepsis, multiple sclerosis, arthritis, blood clotting disorders, stroke, bacterial infections, autoimmune diseases, respiratory syncytial virus (RSV) infections, degenerative myopia, diabetes, macular degeneration, and many obscure diseases. The influenza virus has no approved monoclonal antibody drugs because of its high mutation rate, though a 2024 study[16] reported a promising new approach for a flu-targeting monoclonal antibody. Its long-term effectiveness remains to be seen.

Monoclonal antibodies were initially highly effective against SARS-CoV-2; however, variants of concern significantly reduced their effectiveness over time. Figure 7 summarizes the timeline of monoclonal antibody approvals and when they were rendered ineffective by emerging viral variants.

Interestingly, a 2024 study reported that several non-neutralizing antibodies provided protection against SARS-CoV-2 in different animal models.[17]

The FDA-approved monoclonal antibodies were highly effective when administered early and were considered safe for use in pregnant women. Once taken, the FDA recommended delaying COVID-19 vaccination by 90 days, as monoclonal antibodies could interfere with the immune response to the vaccines. Effectiveness data for these antibodies are as follows:

Table 6. Statistics on antivirals in COVID-19 clinical trial data and therapeutic articles

Category	ClinicalTrials.gov			Google Scholar	"The Mouse That Roared"
	Total	Completed	Results		
Approved therapeutics					
Antiviral	736	304	102	3,200,000	2331
Spike protein monoclonal antibody[a]	99	39	18	24,400	497
Casirivimab/imdevimab[b]	25	8	11	6830	38
Sotrovimab[b]	24	9	10	5720	53
Tixagevimab/cilgavimab[b]	18	12	6	4230	39
Mpro				18,900	502
Paxlovid	45	14	7	9780	176
RdRp[c]				23,300	193
Molnupiravir[c]	20	7	5	11,000	107
Remdesivir[d]	108	51	26	41,200	73
Promising therapeutics					
Innate immunity					
Interferon	68	36	0	491,000	37
Other types					
ACE2	31	10	2	63,700	102
Simvastatin	4	1	0	16,900	8
Herbs (will be discussed later)	-	-	-	-	-
Limited-effectiveness therapeutics					
Renin-angiotensin system inhibitors	9	2	0	38,000	4
Convalescent plasma	175	87	30	42,300	48
Favipiravir	65	36	9	23,100	26

Notes: [a]There are 71 nanobodies that are reviewed in "The Mouse That Roared" but are not yet tested in United States Food and Drug Administration (FDA)-approved clinical trials. [b]Numerous papers discussed multiple monoclonal antibodies. [c]Numerous papers discussed RdRp therapeutics with other therapeutics, e.g., Paxlovid and monoclonal antibodies. [d]Twenty articles related to molnupiravir that are reviewed in "The Mouse That Roared" were co-studied with Paxlovid. Data sourced from ClinicalTrials.gov, Google Scholar, and "The Mouse That Roared" (R. L. Martin, unpublished report, 2025). Abbreviations: ACE2: Angiotensin-converting enzyme 2; Mpro: Main protease; RdRP: RNA-dependent RNA polymerase.

- Casirivimab with imdevimab: A 2022 study reported that among seronegative patients, 396 (24%) of 1633 patients receiving casirivimab and imdevimab died within 28 days, compared to 452 (30%) of 1520 patients receiving usual care (rate ratio [RR]: 0.79, 95% CI: 0.69 – 0.91).[18]

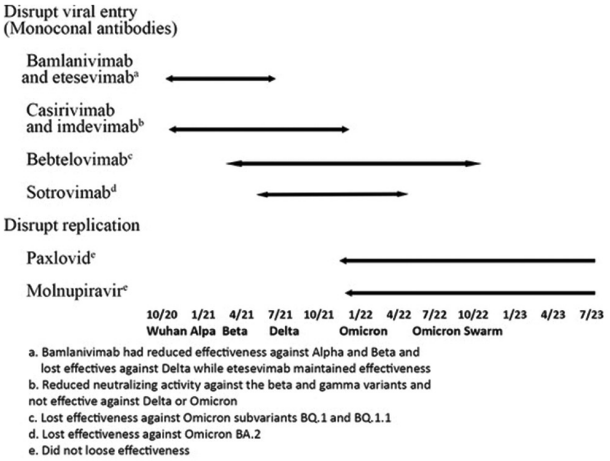


Figure 7. Timeline of monoclonal antibodies' effectiveness against Severe Acute Respiratory Syndrome Coronavirus 2 variants.
Notes: [a]Bamlanivimab has reduced effectiveness against alpha and beta variants and lost effectiveness against the delta variant, while etesevimab remains effective. [b]Reduced neutralizing activity against the beta and gamma variants, and not effective against delta and omicron variants. [c]Lost effectiveness against omicron subvariants BQ.1 and BQ.1.1. [d]Lost effectiveness against the omicron subvariant BA.2. [e]Did not lose effectiveness.

- Bamlanivimab in conjunction with etesevimab: A 2021 study reported that by day 29, 11 of 518 patients (2.1%) in the bamlanivimab–etesevimab group experienced COVID-19-related hospitalization or death, compared to 36 of 517 patients (7.0%) in the placebo group (absolute risk difference: −4.8 percentage points; 95% CI: −7.4 – −2.3; relative risk difference: 70%; $p<0.001$).[19] No deaths occurred in the bamlanivimab–etesevimab group, whereas 10 deaths occurred in the placebo group. Effectiveness was lost against Beta and Gamma variants.
- Sotrovimab: A 2021 study reported an 85% relative risk reduction in hospitalization or death (97.24% CI: 44 – 96%).[20] While it retained some effectiveness against Omicron BA.1 and BA.2, later Omicron subvariants rendered it ineffective.
- Evusheld (tixagevimab and cilgavimab): A 2022 study reported that follow-up at a median of 6 months showed a relative reduction in infection risk of 82.8% (95% CI: 65.8 – 91.4).[21] Although initially effective against Omicron BA.1 and BA.2, it was rendered ineffective by later Omicron subvariants. It was extensively used for infection protection.

The NIH COVID-19 Treatment Guidelines have noted that these monoclonal antibodies are no longer effective. At present, Llama, hamster, or ferret monoclonal antibodies and nanobodies have been developed to target:
(i) The neuropilin-1 binding domain

(ii) The furin/transmembrane serine protease 2 (TMPRSS2) cleavage site; and
(iii) Several structural and NSPs.

However, none of these candidates progressed to large-scale clinical trials.

(a) Inhibition of viral replication proteins

Several viral proteins and protein complexes are essential for viral replication. Figure 8 illustrates SARS-CoV-2 proteins, adopted from a *Cell* paper.[22]

(b) NSP 5/Mpro

The virus replicates by hijacking the host's replication machinery and materials. It produces two long polyproteins, ORF1a and ORF1b, which are cleaved into individual NSPs. This cleavage is initiated by the host's relatively inefficient enzymes and completed by two viral proteases. Mpro (NSP5) cleaves the ORF1a polyprotein, and its inhibition effectively halts viral replication. Likewise, inhibiting PLpro (NSP3) also disrupts viral replication. Currently, there are no approved drugs targeting PLpro.

6.1.2. Paxlovid

Paxlovid, which combines two drugs – nirmatrelvir and ritonavir – is the most effective FDA-approved COVID-19 antiviral. Nirmatrelvir, originally tested against MERS in 2012, inhibits Mpro by cleaving it. Ritonavir, although an antiviral used in acquired immunodeficiency syndrome (AIDS) treatment, is included primarily to boost nirmatrelvir's effectiveness. The FDA granted Paxlovid Emergency Use Authorization on December 21, 2021, and full approval on May 23, 2023. To date, no Mpro mutation has rendered it ineffective. China developed a Paxlovid analog, azvudine, and another Mpro drug, leritrelvir.

(a) Patient suitability

Paxlovid is not suitable for everyone because of potential drug interactions involving ritonavir. These interactions may occur with commonly prescribed medications, necessitating caution. The FDA Paxlovid Drug Interactions and the University of Liverpool Drug Interactions websites provide detailed assessments of these interactions. These resources categorize interactions based on clinical risk, including when Paxlovid should not be used, when it can be used with close monitoring, or when certain medications – such as simvastatin – must be paused before initiating treatment. Paxlovid is considered safe for use during pregnancy.

(b) Effectiveness against COVID-19

There have been numerous studies reporting varying results. A 2022 study presented the Phase 3 trial results in adults and reported:[23]

- An 89.1% reduction in hospitalization risk. No deaths occurred in the Paxlovid group, compared to 1% mortality in the placebo group
- Diarrhea was seen in 3.1% of participants taking Paxlovid, compared to 1.6% in the placebo group
- A strong bitter or metallic taste, later called Paxlovid mouth, was reported by 5.6% of participants taking Paxlovid. Sucking on sweets or using saccharin was found to help. Only 0.03% in the placebo group reported a similar taste.

A 2023 study highlighted the importance of early treatment.[24] It found that Paxlovid's effectiveness in preventing hospitalization or death differed greatly depending on how soon it was administered:

- Within 30 days of a positive test for SARS-CoV-2, effectiveness was 53.6% (95% CI: 6.6 – 77.0)

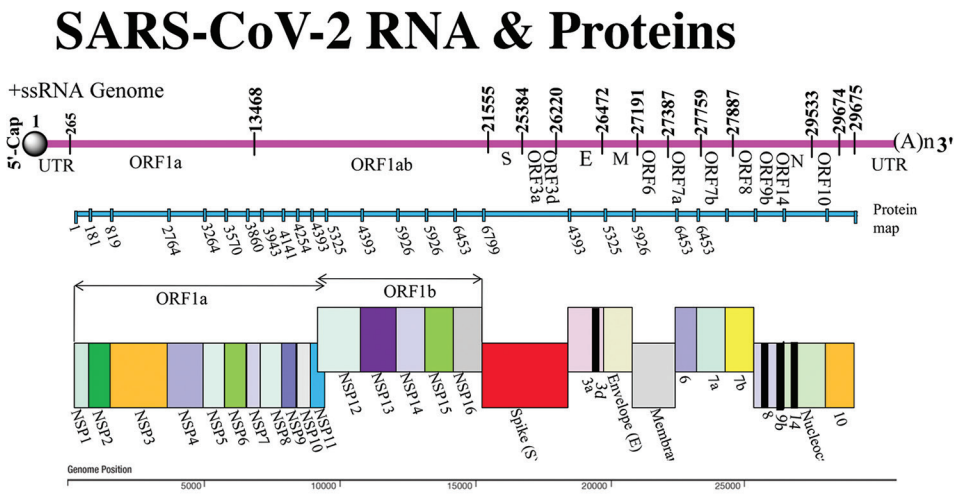


Figure 8. Severe Acute Respiratory Syndrome Coronavirus 2 proteins. Adopted from Yadav *et al.*[22]

- Within 5 days of symptom onset, effectiveness was 79.6% (95% CI: 33.9 – 93.8)
- On the 1st day of symptom onset, effectiveness was 89.6% (95% CI: 50.2 – 97.8).

According to NIH guidelines, treatment should begin promptly and within 5 days of the onset of symptoms.

(c) Viral rebound

Viral rebound occurs in 2 – 5% of individuals who take Paxlovid. The phenomenon is not well understood, and studies have reported widely differing results. According to the CDC,[25] among those with a virologic response by day 5, viral rebound was observed in 6.4 – 8.4% of Paxlovid recipients and 5.9 – 6.5% of placebo recipients during both the 2021 pre-Omicron and 2022 Omicron periods.

(d) Paxlovid underutilization

Due to cost concerns, fear of rebound, and side effects, Paxlovid remains significantly underutilized. A 2022 CDC report[26] found that among 699,848 adults aged 18 and older who were eligible for Paxlovid during April – August 2022, only 28.4% received a Paxlovid prescription within 5 days of their COVID-19 diagnosis. Furthermore, utilization was even lower among individuals in lower socioeconomic groups, despite government coverage of the medication during that time.

In October 2022, *The New York Times*[27] reported that Paxlovid was used by political affiliation and suggested that higher COVID-19 death rates in the red states may be linked to Paxlovid underutilization. Figure 9 summarizes US Department of Health and Human Services data on Paxlovid prescriptions in relation to the 2020 presidential election margin between Biden and Trump.

(e) NSP 12/RdRp

Unlike many viruses, including the influenza virus, SARS-CoV-2 has a replication mechanism that includes error correction, enhancing its replication fidelity. Two FDA-approved therapeutics target this process by interfering with the NSP12 (RdRp), a key component of the virus's replication complex:

(i) Remdesivir is an intravenous, hospital-administered therapeutic. It previously showed effectiveness against hepatitis C and RSV in 2009, Ebola in 2014, and Marburg virus disease in 2015. The FDA approved it for COVID-19 treatment on October 22, 2020

(ii) Lagevrio (molnupiravir) is a tablet therapeutic. It had previously shown effectiveness against influenza, Ebola, chikungunya, and various coronavirus-induced diseases, including MERS. The FDA approved it for COVID-19 use on December 23, 2021.

6.1.3. Remdesivir

A 2020 study reported remdesivir's effectiveness against COVID-19,[28] as shown in Table 7.

A 2024 study reported that remdesivir was associated with an absolute risk reduction of 6.4% and a relative risk reduction of 66% for all-cause hospitalization or death.[29] It is often taken with Paxlovid. To date, RdRp mutations have not yet disabled remdesivir's effectiveness.

Remdesivir can help keep patients alive for prolonged periods while they remain COVID-19 positive. However, extended infections provide an ideal environment for viral mutations. Five papers cited in "The Mouse That Roared" (R. L. Martin, unpublished report, 2025) reported that substantial viral mutations occurred in remdesivir-treated patients.

The NIH COVID-19 Treatment Guidelines recommend remdesivir for use within 7 days of symptom onset in a hospitalized setting, often in combination with other drugs. However, they recommend Paxlovid as the preferred option when appropriate.

6.1.4. Lagevrio (molnupiravir)

A 2021 study reported Lagevrio's effectiveness against COVID-19,[30] as summarized in Table 8.

A 2022 medRxiv preprint[31] reported a retrospective study of 92 million patients, of whom 11,270 received Paxlovid and 2374 received molnupiravir within 5 days of COVID-19 symptom onset. The results are summarized in Table 9.

Table 7. Remdesivir's effectiveness against COVID-19

Medication effectiveness measures	Remdesivir	Placebo
Recovery time (days)	10	15
Mortality by day 29 (%)	11.4	15.2
Serious adverse events (%)	24.6	31.6

Table 8. Lagevrio's (molnupiravir) effectiveness against COVID-19

Medication effectiveness measures	Molnupiravir	Placebo
Hospitalization or death by day 29 (%)	6.9	9.7
Serious adverse events (%)	30.4	31.6

Table 9. Molnupiravir's effectiveness against COVID-19

Medication effectiveness measures	Paxlovid		Molnupiravir	
	7 Days	30 Days	7 Days	30 Days
Symptoms (%)	2.31	5.87	3.75	8.21
Hospitalization (%)	0.44	0.77	0.84	1.39
Rebound[a] (%)	3.53	5.40	5.86	8.59

Note: [a]Patients with COVID-19 rebound had a significantly higher prevalence of underlying medical conditions than those without.

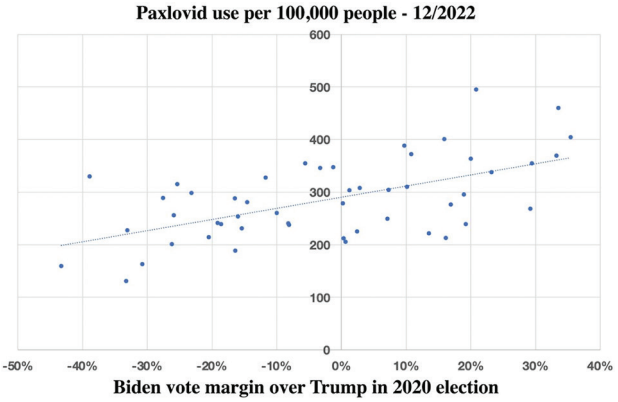


Figure 9. State-level Paxlovid usage rates by Biden–Trump vote margin in the 2020 presidential election. Graph created by the author using United States Department of Health and Human Services data.

All comprehensive studies reported greater effectiveness for Paxlovid. However, molnupiravir is suitable for a broader patient population. The NIH COVID-19 Treatment Guidelines recommended molnupiravir only when Paxlovid and remdesivir are not appropriate treatment options.

6.1.5. Mutations in SARS-CoV-2

A 2024 study reported that molnupiravir induced SARS-CoV-2 mutations,[32] as summarized in Figure 10.

Molnupiravir raised concerns about its potential to alter human DNA. However, the FDA reported that the post-treatment genotoxicity data imply a low risk of DNA damage. Nonetheless, the FDA issued the following precautions:

- Do not use in pregnant patients unless no alternative treatments are available and the potential benefits outweigh the risks
- Use effective contraception during molnupiravir treatment and for a period after completing the course
- Restrict use to adults aged 18 years and older.

6.2. Promising therapeutics

6.2.1. Interferon

The most discussed anti-inflammatory cytokines in the context of COVID-19 are interferons (IFNs). They "interfere" with viral replication to protect cells from infection. Although no approved IFN drugs are available for COVID-19 treatment, "The Mouse That Roared" (R. L. Martin, unpublished report, 2025) identified multiple potential drugs targeting IFNs, including IFN-beta (IFN-β), IFN-β1a, IFN-γ, IFN-λ2, and IFN-α16. A 2023 study reported that IFN-α2b reduced lung injury by 50% and decreased the odds of developing severe COVID-19 by a factor of five.[33]

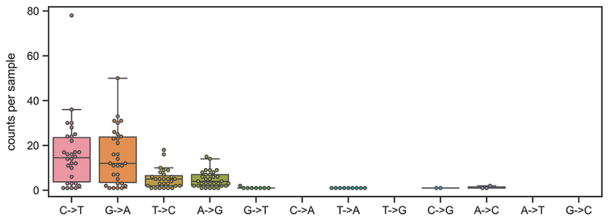


Figure 10. Molnupiravir-induced mutations in severe acute respiratory syndrome coronavirus 2. Reprinted from Gruber *et al.*[31]

The NIH COVID-19 Treatment Guidelines provided the following recommendations regarding IFN therapies:

- Recommended against the use of IFN-α or IFN-β for non-hospitalized patients with mild-to-moderate COVID-19, except in clinical trials
- Recommended against the use of IFN-α, except in a clinical trial, and IFN-β for hospitalized patients
- Made no recommendation for or against the use of IFN-λ.

While some IFN therapeutics showed early promise, none received FDA approval for the treatment of COVID-19.

6.2.2. ACE2 inhibitors

The primary way for SARS-CoV-2 to enter human cells is when its spike protein binds to a cell's ACE2 receptor, facilitating viral entry. Monoclonal antibodies interfere with this process by binding to the spike protein and blocking its interaction with ACE2 receptors. Several promising ACE2-based approaches were discussed in "The Mouse That Roared" (R. L. Martin, unpublished report, 2025), including:

(i) Biochemically altering ACE2 receptors to prevent spike protein binding
(ii) Reducing ACE2 receptor expression on host cells to limit viral entry points
(iii) Using ACE2 receptor-binding particles to pre-occupy receptors and block viral binding
(iv) Deploying ACE2 decoys – such as nanoparticles-bound, soluble, or inhaled forms – to bind and neutralize the spike protein before it can reach actual cells.

Although these strategies demonstrated excellent success rates across viral variants, little progress has been made in commercializing ACE2 inhibitors. The NIH COVID-19 Treatment Guidelines are currently silent on ACE2-based inhibitors.

6.2.3. Simvastatin

Many individuals take statins to manage cholesterol levels. Of the various statins tested, only simvastatin showed

a modest effect on COVID-19 outcomes in selected studies. A 2023 study evaluated simvastatin in critically ill COVID-19 patients.[34] Although the study ended early due to declining case numbers, the results indicated that simvastatin did not meet the pre-specified criteria for superiority compared to the control group.

6.2.4. Herbs

Table 10 summarizes the statistics of herbal therapeutic articles on COVID-19 collected from ClinicalTrials.gov, Google Scholar, and "The Mouse That Roared" (R. L. Martin, unpublished report, 2025).

Table 11 presents a breakdown of the herbs into various categories.

The February 2023 COVID-19 Treatment Guidelines (https://www.ncbi.nlm.nih.gov/books/NBK570371/pdf/Bookshelf_NBK570371.pdf) from China span 26 pages, with 10 pages dedicated to traditional Chinese medicines. These guidelines also included "Western" therapeutics, such as Paxlovid. In contrast, the NIH COVID-19 Treatment Guidelines mention herbs only in the context of potential medical contraindications. They note that while no herbal therapies are currently approved, many show promise.

6.3. Limited-effectiveness therapeutics

6.3.1. Renin-angiotensin system inhibitors

Given that the cytokine storm and the bradykinin storm result from disruption of the renin-angiotensin system, it is reasonable to speculate that preventing this disruption could serve as an effective antiviral strategy. However, four papers discussed in "The Mouse that Roared" (R. L. Martin, unpublished report, 2025) reported controversial results on this approach.

6.3.2. Convalescent plasma

Blood plasma is the yellowish liquid component of blood that suspends the blood cells and proteins throughout the body. The first Nobel Prize in Physiology and Medicine was awarded in 1901 to Emil von Behring for successfully using antibodies from the plasma of animals that had recovered from diphtheria to treat diphtheria patients.

Plasma therapy is believed to have reduced mortality by half during the 1918 Spanish Flu, especially when administered early. It was later used against measles in the 1930s, the Korean hemorrhagic fever in the 1950s, and has been one of the most effective treatments for Ebola.

In 2020, Arturo Casadevall, a Johns Hopkins Bloomberg Distinguished Professor of Molecular Microbiology and Immunology and the department chairman, led a strong advocacy campaign urging further investigation into COVID-19 plasma therapy.

(a) Conflicting results

Convalescent plasma trial results have been mixed. A 2023 study analyzed 19 trials and reported that the estimated mortality relative to placebo was 0.94 (95% CI: 0.81 – 1.08, p=0.33).[35]

The NIH COVID-19 Treatment Guidelines concluded that there is insufficient evidence to recommend either for or against the use of high-titer convalescent plasma in hospitalized or non-hospitalized immunocompromised patients.

6.3.3. Favipiravir

Favipiravir, though of uncertain effectiveness and not approved in the US, is used in Japan to treat influenza. For COVID-19, it was thought that favipiravir might inhibit

Table 10. Statistics on herbal therapeutic articles on COVID-19

Medication effectiveness measures	ClinicalTrials.gov			Google Scholar	"The Mouse That Roared"
	Total	Completed	Results		
Herbs	15	6	0	57,000	263
Traditional Chinese medicine[a]	21	7	0	447,000	53

Notes: [a]Included the total herb count; Data from ClinicalTrials.gov, Google Scholar, and "The Mouse That Roared" (R. L. Martin, unpublished report, 2025), as of November 01, 2024.

Table 11. Types of herbal therapeutics against COVID-19

Medication effectiveness measures	All	Herbs, excluding TCM			TCM		
		Antiviral	Mainly inflammation treatment	Antiviral and inflammation treatment	Antiviral	Treating mainly inflammation	Antiviral and inflammation treatment
Total	314	179	58	21	24	28	4
Mpro	45	36	-	1	8	-	0
RdRp	12	9	-	0	3	-	0

Note: Statistics from ClinicalTrials.gov, Google Scholar, and "The Mouse That Roared" (R. L. Martin, unpublished report, 2025), as of November 01, 2024.
Abbreviations: Mpro: Main protease; RdRp: RNA-directed RNA polymerase; TCM: Traditional Chinese medicine.

the viral RdRp and potentially disrupt the envelope and ORF7a proteins.

A 2020 study reported that among 35 patients treated with favipiravir and 45 control patients, the median viral clearance time was shorter with favipiravir – 4 days (interquartile range 2.5 – 9 days) versus 11 days (interquartile range 8 – 13 days).[36] The study also reported 91.43% improvements in chest computed tomography scans of favipiravir-treated patients, compared to 62.22% improvement in the control group. However, several clinical trials concluded that favipiravir did not significantly improve clinical outcomes, although it may offer some symptom relief in mild to moderate cases. The NIH COVID-19 Treatment Guidelines only referenced favipiravir in the context of one clinical trial that also included ivermectin.

6.4. Other antivirals with insufficient data to determine effectiveness

In addition to the antivirals already discussed, approximately 550 articles that address other parts of the viral lifecycle were reviewed in "The Mouse That Roared" (R. L. Martin, unpublished report, 2025). These therapeutics employed a wide range of mechanisms, such as utilizing amino acids, peptides, aptamers, short RNA, microRNA, ultraviolet light in lungs, and plasma-activated water, to disrupt viral biochemical processes – either by altering molecular shapes or damaging them through enzymes such as proteases or kinases. A significant number of therapeutics focused on interfering with the N-protein's glycans. Extensive drug and compound screening efforts were reported, with databases including, e.g., 350,000, 33,590, 22,000, 18,000, 6,710, 6,218, 2,100, 1,900, 1,796, and 850 candidates. These potential treatments were administered through diverse methods such as chewing gum, nasal spray, mouthwash, tablets, and injections.

The drug compounds and sources explored included: hydrogen sulfide compounds, sodium chloride, zinc oxide, cerium oxide, hydrophobic C60, copper, gold, silver, chlorine dioxide, copper ferrite, boron, nitric oxide, selenium, Vitamin B1 and B12 supplements, TMPRSS2 inhibitors, phosphatidic acid, nucleic acids, antiandrogens, human breast milk, pluripotent stem cells, earthworms, chewing gum, shark immune cells, mesenchymal stem cells, fungi, bacteria such as *Escherichia coli*, marine sponges, scorpion venom, IFNs, natural killer cells, sea cucumbers, mink lung epithelial cells, clustered regularly interspaced short palindromic repeats (CRISPR) technologies for identification or modification, cow's milk, monoclonal antibodies, coffee, bee venom, electric fields, mouthwash, purified immunoglobulin G, antiprotozoal agents, emetics, spider hemocytes, *Salamandra* species, sweet potato roots, oriental wasps, human defensins, bile acids, antibiotics, hen egg yolks, bovine herpesvirus, male contraceptives, cardiac imaging agents, and inhaled heparin.

Many drugs originally developed for other diseases showed some effectiveness against COVID-19. These diseases/symptoms include gas, leprosy, irritable bowel syndrome, tapeworm infections, epilepsy, gout, vaginal infections, hepatitis, AIDS, parasitic diseases, sleeping sickness, depression, anticonvulsant conditions, constipation, hyponatremia, overactive bladder, circadian rhythm disorders, cystinosis, influenza, fungal bacterial infections, macular degeneration, asthma, malaria, RSV, cardiac imaging conditions, ring-stage parasites, psychotic disorders, diuretic needs, kidney damage, human papillomavirus infection, bipolar disorder, schizophrenia, anxiety, migraines, tranquilizer use, high cholesterol, hepatitis C, pulmonary fibrosis, gallstones, liver disease, type I Gaucher disease, Fabry disease, anemia, hypovolemia, herpes, pancreatitis, reflux esophagitis, weight loss, hypertension, ectopic pregnancies, abnormal hemoglobin, allergies, hay fever, the common cold, rheumatoid arthritis, tachycardia, shortness of breath, pale skin, cold extremities, dark urine, jaundice, mitochondrial oxidative stress, lung transplantation, antiandrogen conditions, lactate-lowering needs, viral hemorrhagic fevers, throat and tonsils infections, ulcerative colitis, diabetic kidney disease, lupus, and methemoglobinemia.

7. Suppression of hyperinflammation

At the hyperinflammation stage (suppress hyperinflammation phase in Figure 1), the virus has replicated extensively and is now resulting in one of two outcomes:

(i) Mild-to-moderate COVID-19, which typically requires no further treatment
(ii) Severe COVID-19 may require hospitalization and carries a risk of death.

Long COVID can develop after either outcome, though it is more commonly associated with severe cases.

7.1. Inflammation

Inflammation is the body's natural response to injury or infection. Its purpose is to eliminate the cause of harm, remove damaged cells, and initiate healing. The inflammatory process involves:

(i) Recognition of harmful stimuli, such as physical injury or pathogens such as SARS-CoV-2
(ii) Release of signaling molecules, such as histamines and cytokines
(iii) Recruitment of immune cells – particularly white blood cells such as neutrophils and macrophages – to neutralize pathogens and remove cellular debris.

Hyperinflammation refers to excessive inflammation. In COVID-19, hyperinflammation can cause significant damage throughout the body, as shown in Figure 11, reprinted from a 2021 COVID article.[37]

7.1.1. Hyperinflammation causes

Hyperinflammation in COVID-19 has two primary causes:

(i) When SARS-CoV-2 binds to ACE2 receptors, it dysregulates the renin-angiotensin-aldosterone system, which plays important roles in controlling inflammation and blood pressure. Through a complex process, this dysregulation results in an overproduction of cytokines, which are small proteins that act as signaling molecules in the immune system. This excessive cytokine release is known as a cytokine storm. There are hundreds of cytokines, of which the most prominent pro-inflammatory cytokines are tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-6, IL-17, IL-12, IL-23, and IFN-γ. Although cytokines work together to amplify inflammation and coordinate immune responses, their overproduction can lead to excessive inflammation and tissue damage, as seen in autoimmune diseases, cancers, infections, and physical damage.

(ii) The innate immune system's effector cells are damaged, releasing cytokines. This damage also promotes viral replication, as it generally takes 4 – 6 days before the adaptive immune system becomes fully activated.

If a patient reaches the point of hospitalization, their situation becomes critical. Hyperinflammation is especially difficult to treat because suppressing inflammation may impair the body's defense mechanisms, the underlying biology is highly complex and multifactorial, it is self-sustaining, there is significant individual variability in response, and the available treatments often carry side effects.

Numerous COVID-19 hyperinflammation drugs also target comorbidities frequently seen in COVID-19 patients, such as cancer, autoimmune diseases, obesity, diabetes, and gut microbiome imbalances. This overlap creates a complex interplay between the drugs' mechanisms and the observed clinical outcomes. The statistics on anti-inflammatory therapeutic articles for COVID-19 acquired from ClinicalTrials.gov, Google Scholar, and "The Mouse That Roared" (R. L. Martin, unpublished report, 2025) are shown in Table 12.

The two therapeutic approaches to hyperinflammation are:

(i) Address the cause, i.e., prevent inflammation by protecting the renin-angiotensin system and the innate immune system

(ii) Address the result, i.e., reduce inflammation.

Table 12. Statistics on anti-inflammatory therapeutic articles

Medication effectiveness measures	ClinicalTrials.gov			Google Scholar	"The Mouse That Roared"[a]
	Total	Completed	Results		
Prevent inflammation	241	97	22	214,000	457
Suppress inflammation					
Approved					
Tocilizumab	75	31	7	38,600	43
Anakinra	25	13	3	14,600	16
Baricitinib	27	8	3	13,400	24
Promising					
Corticosteroid	79	34	3	127,000	65
Dexamethasone	93	40	7	131,000	56
Spirulina	2	2	1	7,080	3
Metformin	9	2	1	42,600	24

Notes: [a]Many papers discussed several drugs; Statistics from ClinicalTrials.gov, Google Scholar, and "The Mouse That Roared" (R. L. Martin, unpublished report, 2025), as of November 1, 2024.

7.2. Inflammation prevention

No therapeutics to prevent inflammation have been approved for use.

7.2.1. Promising therapeutics

There are several promising therapeutics for preventing inflammation in COVID-19.

(a) Pro-inflammatory cytokine inhibition

Interleukins, the cytokines with primarily pro-inflammatory impacts, modulate the growth, differentiation, and activation of immune cells during inflammatory and immune responses. They stimulate immune cell recruitment and activation, increase vascular permeability, and induce fever – all of which are critical for fighting off invading pathogens. However, some ILs, such as IL-1, IL-4, IL-6, IL-10, IL-11, and IL-13, can have anti-inflammatory effects.

Despite its potential anti-inflammatory roles, IL-6 is frequently identified as a particularly pro-inflammatory IL in the context of COVID-19. A 2023 study reported that inhibiting IL-6 with Jusvinza reduced mortality to 10% in the treated group, compared to 60% in the untreated group.[38] Many traditional Chinese medicine therapies target IL-6 modulation.

Articles reviewed in "The Mouse That Roared" (R. L. Martin, unpublished report, 2025) addressed a broad range of ILs, such as IL-1Ra, IL-1β, IL-2C, IL-7, IL-17i, IL-18, IL-23, IL-23i, and IL-33. Meanwhile, the NIH COVID-19

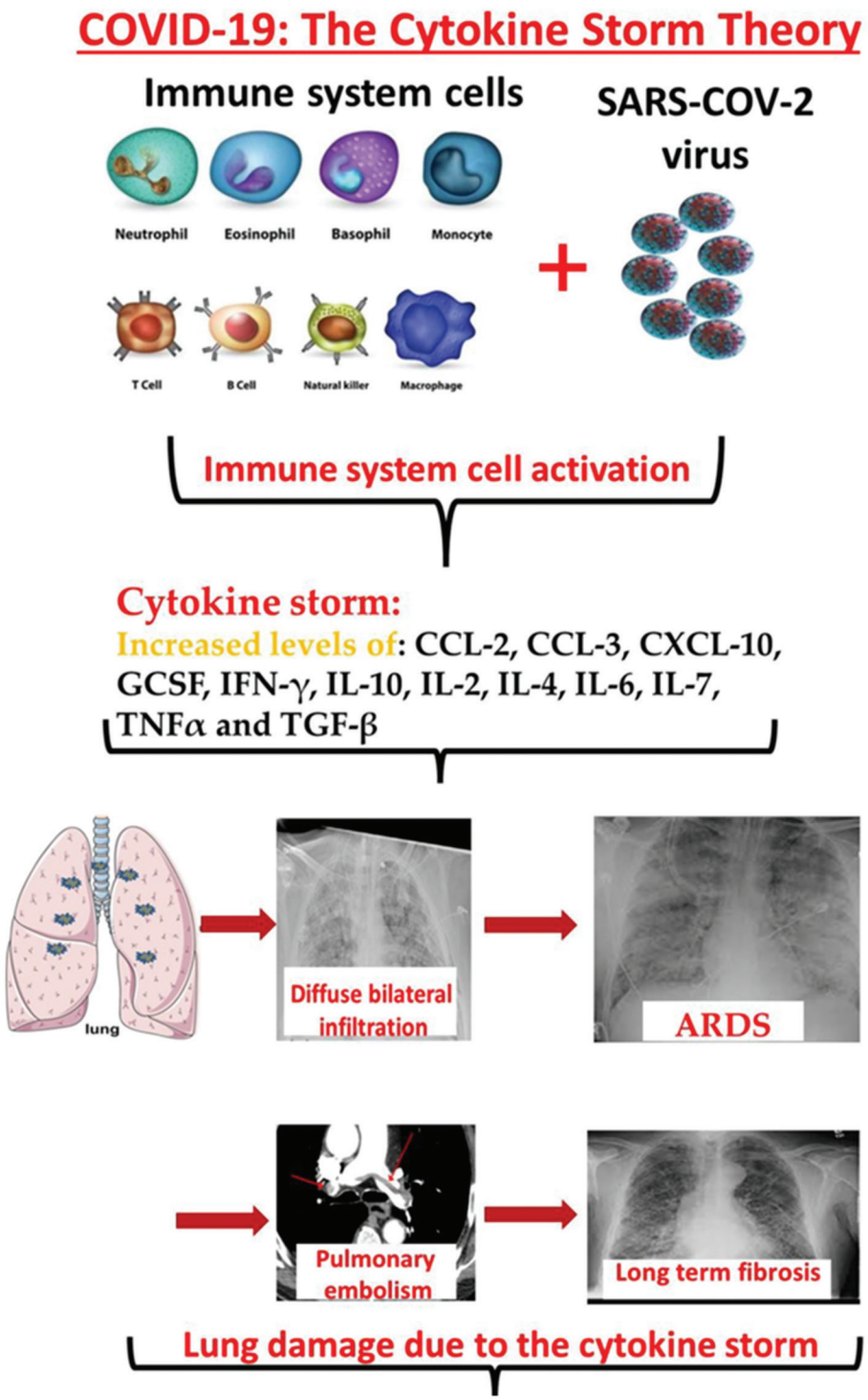


Figure 11. The cytokine storm theory in COVID-19. Reprinted from Venegas-Rodríguez *et al.*[37]
Abbreviations: ARDS: Acute respiratory distress syndrome; CCL: Chemokine (C-C motif) ligand; CXCL: Chemokine (C-X-C motif) ligand; GCSF: Granulocyte-colony stimulating factor; IFN: Interferon; IL: Interleukin; TNF: Tumor necrosis factor.

Treatment Guidelines address IL-6 suppression in hospitalized COVID-19 patients and recommend tocilizumab in combination with dexamethasone for certain cases.

(b) Effector cell protection

A few of the papers reviewed in "The Mouse That Roared" (R. L. Martin, unpublished report, 2025) discussed therapeutics aimed at reducing the inflammatory impacts on innate immune system effector cells. For example, macrophages were targeted with hydroxyl-polyamidoamine dendrimer-N-acetyl cysteine conjugate, natural killer cells were supported with 7DW8-5 glycolipid, TNF was modulated through nanochelating technology, neutrophils were addressed with sivelestat, and most importantly, neutrophil extracellular traps (NETs) were disrupted using thiocyanate and DNA proteases. In addition, a 2024 study reported that infusing cytotoxic T-cells led to viral elimination in patients, achieving more than 88% clearance in 4 days and more than 99% in 14 days.[39]

(c) Complement system enhancement

The complement system enhances the abilities of antibodies and phagocytic cells to ingest pathogens, promotes inflammation, and attacks the pathogen's cell membrane. It is dysregulated in COVID-19. A 2020 study reported that the Janus kinase (JAK)1/JAK2 inhibitor ruxolitinib helped normalize complement system activity.[40] The NIH COVID-19 Treatment Guidelines do not address the complement system.

7.2.2. Ineffective therapeutics

There are numerous ineffective therapeutics for preventing inflammation in COVID-19.

(a) Renin-angiotensin system inhibitors

A dysregulated renin-angiotensin system triggers the cytokine storm. ACE inhibitors, angiotensin receptor blockers, and direct renin inhibitors were trialed as potential treatments, but none reported encouraging results. In addition, certain blood pressure drugs interact with the renin-angiotensin system. The NIH COVID-19 Treatment Guidelines recommend that individuals already taking these drugs continue their use, but do not recommend initiating them specifically for COVID-19 treatment.

7.3. Hyperinflammation treatment

The approved and promising therapeutics for hyperinflammation treatment in COVID-19 are discussed in this section.

7.3.1. Approved therapeutics

Multiple medications have been used in treating hyperinflammation in COVID-19.

(a) Tocilizumab

Tocilizumab is a monoclonal antibody immunosuppressant that targets IL-6. Approved for use in Japan in 2008, it is primarily used to treat rheumatoid arthritis. It targets pro-inflammatory cytokines, including TNF-α, IL-6, IL-1, and IL-17, as well as immune cell surface receptors. The FDA granted tocilizumab Emergency Use Authorization for COVID-19 on December 21, 2022.

A 2021 study reported that eight clinical trials produced mixed outcomes.[41] Subsequent studies reported that tocilizumab:

(i) improved outcomes, including survival (36% vs. 26%)[42]

(ii) had no effect on disease severity or mortality.[43]

(b) Anakinra

Used to treat rheumatoid arthritis, anakinra is a recombinant, slightly modified version of a human IL-1 receptor antagonist. It targets pro-inflammatory cytokines, such as TNF-α, IL-6, IL-1, and IL-17, as well as immune cell surface receptors. Anakinra was first used for familial Mediterranean fever in 1998. The FDA granted it Emergency Use Authorization for COVID-19 on November 8, 2022, one year after the EU.

A 2021 paper summarized six clinical trials, reporting that anakinra showed a survival benefit when administered without dexamethasone (odds ratio [OR]: 0.23, 95% CI: 0.12 – 0.43), but not when given alongside dexamethasone (OR: 0.72, 95% CI: 0.37 – 1.41).[44] Other studies did not demonstrate strong effectiveness for anakinra.

(c) Baricitinib

Baricitinib was approved by the FDA for the treatment of rheumatoid arthritis in 2017. It blocks JAK enzymes, which are critical in the signaling pathways of several pro-inflammatory cytokines, such as IL-6 and IFN-γ. The FDA granted baricitinib Emergency Use Authorization for COVID-19 on May 10, 2022.

A 2020 study reported that patients receiving baricitinib had a median recovery time of seven days (95% CI: 6 – 8), compared to eight days (95% CI: 7 – 9) for controls.[45] Baricitinib also improved clinical status at day 15, with a 30% higher odds of improvement (OR: 1.3, 95% CI: 1.0 – 1.6). Among patients who were receiving high-flow oxygen or non-invasive ventilation at enrollment, the median recovery time was 10 days in the combination treatment group versus 18 days in controls (RR for recovery: 1.51, 95% CI: 1.10 – 2.08). The 28-day mortality was 5.1% in the combination group versus 7.8% in the control group.

The NIH COVID-19 Treatment Guidelines noted that the use of immunomodulators, such as dexamethasone,

JAK inhibitors (e.g., baricitinib and tofacitinib), IL-6 inhibitors (e.g., tocilizumab and sarilumab), TNF inhibitors (e.g., infliximab), and abatacept (also used for rheumatoid arthritis), to treat COVID-19 may increase the risk of infectious complications. However, when these therapies are used appropriately, the benefits outweigh the risks.

7.3.2. Promising therapeutics

The promising therapeutics include glucocorticoids, spirulina, and metformin.

(a) Glucocorticoids

Glucocorticoids are steroid hormones that exert diverse and potent immunosuppressive effects by downregulating pro-inflammatory cytokines, such as various ILs, and by blocking inflammatory signaling pathways.

Dexamethasone, the most frequently used glucocorticoid, was often administered in combination with antivirals. A 2020 study reported that in the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%, RR: 0.64, 95% CI: 0.51 – 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%, RR: 0.82, 95% CI: 0.72 – 0.94), but not among those who were not receiving support (17.8% vs. 14.0%, RR: 1.19, 95% CI: 0.92 – 1.55).[46]

Other studies reported mortality reductions of 42%, 33%, 32.2%, and 20% (in two separate papers). Nonetheless, dexamethasone use is not without risks. It has been associated with altered gut bacterial compositions and increased incidence of hyperglycemia in diabetic patients. The NIH COVID-19 Treatment Guidelines on dexamethasone noted:

(i) There is a lack of safety and efficacy data on dexamethasone use in outpatient COVID-19 patients, and it may cause harm in these cases
(ii) It should only be used if patients require supplemental oxygen, and should be used in combination with remdesivir.

(b) Spirulina

Spirulina is a type of bacteria that significantly reduces the levels of IL-6, TNF-α, IL-10, and IFN-gamma-induced protein 10. A 2024 study reported that spirulina supplementation was associated with reduced mortality risk in COVID-19 patients.[47] In non-intensive care unit (ICU) patients, the hazard ratio for mortality was 0.13 (95% CI: 0.02 – 0.97), whereas in ICU patients, the hazard ratio was 0.16 (95% CI: 0.05 – 0.48).

(c) Metformin

Clinical trials have reported that metformin reduces mortality by 0%, 40%, 50%, 80%, and 58% in hospitalization or death through 28 days. A June 2023, medRxiv preprint[48] reported that in a Phase 3, randomized, placebo-controlled, outpatient clinical trial, metformin use led to a 42% reduction in emergency room visits, hospitalizations, or death through 14 days, a 58% reduction in hospitalizations or death through 28 days, and a 42% reduction in the incidence of long COVID through 10 months. The NIH COVID-19 Treatment Guidelines noted that:

(i) There is insufficient evidence to recommend either for or against the use of metformin for the treatment of COVID-19 in non-hospitalized patients
(ii) The panel recommends against the use of metformin for the treatment of COVID-19 in hospitalized patients, except in a clinical trial
(iii) Patients with COVID-19 who are receiving metformin for an underlying condition should continue this therapy as directed by their health-care provider.

7.4. Other anti-inflammatory therapeutics with insufficient data to conclude effectiveness

There are 275 remaining anti-inflammatory articles from "The Mouse That Roared" (R. L. Martin, unpublished report, 2025) that have not yet been discussed. They addressed:

(i) Cytokines: IL-6 (main target), IL-2, TNF-α, IL-17, IL-23, IL-7, IFN-γ, TNFα, IL-1β, IL-18, transforming growth factor-β1, IFN-α, IFN-β, angiopoietin-2, and NACHT, LRR and PYD domains-containing protein 3
(ii) Effector cells: Macrophages, cytotoxic T cells, neutrophils, and mast cells
(iii) Kinases, enzymes that catalyze the transfer of a phosphate group from ATP to a specific molecule: JAK, casein kinase 2, TANK-binding kinase 1, and spleen tyrosine kinases
(iv) Miscellaneous targets: Transcription factors, genes that encode proteins that detect products of damaged cells and trigger an immune response, gasdermin D inhibitors, exosomes, adenine dinucleotide metabolism, and NETs.

These therapeutics encompass numerous ingredients or mechanisms: cluster of differentiation 24, N-protein antibodies, monoclonal antibodies for selected cytokines, IFNs, genes, CRISPR-modified T cells, stem cell transplants, hydrogen, immunoglobulins, molecules that induce cell death, bacteria, blood purification, plasma exchange, algae, synthetic angiotensin (1 – 7), angiotensin II type 1 receptor-biased ligand, low-dose radiation, low-intensity pulsed ultrasound, pharmacologic stress agents used in cardiac perfusion imaging studies, drugs to maintain

general anesthesia, hyperimmune plasma from sheep, mesenchymal stromal cells from many sources, injectable porous silicon particles, silver, selenium, lithium, sodium nitrate, hydrogen-rich water, cytotoxic T lymphocytes, cellular human amniotic fluid, degalactosylated bovine glycoproteins, activated protein C, Vitamin E, blood filter, and antioxidant enzymes.

These therapeutics address a wide array of diseases:

(i) Autoimmune diseases: Rheumatoid arthritis, ankylosing spondylitis, psoriasis (including plaque psoriasis), Crohn's disease, inflammatory bowel disease, ulcerative colitis, alopecia areata, multiple sclerosis, chronic immune thrombocytopenia, Behçet's disease, eczema, atopic dermatitis, seborrheic dermatitis, gout, and keratoconjunctivitis sicca associated with Sjögren's syndrome. Multiple human diseases, particularly immunosuppressive diseases, such as inflammatory bowel syndrome, are associated with inflammation. According to a 2024 study,[49] based on a 2013 national estimate, 2.7% of US adults were immunosuppressed due to health conditions or medication use. Certain autoimmune drugs are helpful in treating COVID-19 because they target cytokines, autoantibodies, and interfere with cell signaling pathways that drive inflammation.

(ii) Cancer: Bone marrow cancers, small cell lung cancer, leukemias (e.g., chronic myeloid leukemia, acute lymphoblastic leukemia, and chronic myelogenous leukemia), multiple myeloma, prostate cancer (including castration-resistant prostate cancer), high-risk primary or secondary myelofibrosis, testicular and ovarian cancers, glioblastoma multiforme, and myelodysplastic syndromes. Certain cancer drugs are helpful in treating COVID-19 because they target cytokines, exert strong anti-inflammatory effects, and reduce tumor burden, which in turn can decrease the release of pro-inflammatory mediators.

(iii) Other lung diseases: Chronic obstructive pulmonary disease, chronic bronchopulmonary disorders, idiopathic pulmonary fibrosis, acute lung injury, bleomycin lung injury, acute respiratory distress syndrome (ARDS), and tuberculosis.

(iv) Others: Abnormal blood lipid levels, acute pancreatitis, alcohol use disorder, Alzheimer's disease, amyotrophic lateral sclerosis, angina pectoris, chronic hepatitis, chronic kidney disease, diabetes, diabetic kidney disease, disseminated intravascular coagulation, epilepsy, gastroesophageal reflux disease, graft-versus-host disease, heart conditions, hemophagocytic lymphohistiocytosis, high blood pressure, hyperlipidemia, hypertriglyceridemia, lactobezoar, malaria, migraines, nausea, nephrotic syndrome, neuropathic pain, osteoporosis in postmenopausal women, peptic ulcer disease, prion diseases, depression, psychosis, anxiety, schizophrenia, sepsis, solid organ transplant, superficial mycoses, tapeworm infections, viscid or excessive mucus production, and Zollinger–Ellison syndrome.

8. Organ damage suppression

At the organ damage stage (Figure 1), the patient is critically ill, and no highly effective treatments are available. Table 13 summarizes statistics on studies that addressed two key areas of organ-specific treatment in COVID-19, data acquired from ClinicalTrials.gov, Google Scholar, and "The Mouse that Roared" (R. L. Martin, unpublished report, 2025).

8.1. Lungs

As previously noted, lung damage in COVID-19 patients can result from direct viral injury, inflammation, blood clots, and/or lack of oxygen. Oxygenation will be assessed in this section. Once again, timely intervention is the most important factor. The progression of oxygen treatments, from least to most intensive, includes:

(i) Conventional oxygen therapy
(ii) High-flow nasal cannula: Nasal delivery of an adjustable mixture of heated and humidified air and oxygen at rates that exceed spontaneous inspiratory flow
(iii) Mechanical ventilation
(iv) Extracorporeal membrane oxygenation (ECMO).

Table 13. Statistics on studies focusing on organ damage suppression in COVID-19

Medication effectiveness measures	ClinicalTrials.gov	Google Scholar	"The Mouse That Roared"
Lungs			
Approved therapeutics			
Oxygen	25	1,570,000	71
ECMO	3	40,800	52
Vilobelimab	1	446	6
Cardiovascular			
Approved therapeutics			
Anticoagulants[a]	-	-	54
Heparin	12	133,000	32

Notes: [a]Interpreting ClinicalTrials.gov searches must be done carefully. For example, these were the numbers of trials for different but highly related terms:
- "Anti-coagulant" or "anti coagulant": 34
- "Anti coagulant therapy": 31
- "Anti-coagulants": 1.

Statistics from ClinicalTrials.gov, Google Scholar, and "The Mouse That Roared" (R. L. Martin, unpublished report, 2025), as of December 01, 2024.
Abbreviation: ECMO: Extracorporeal membrane oxygenation.

8.1.1. ECMO

ECMO is a mechanically supported ventilation system used for severe COVID-19 respiratory failure. For COVID-19 patients, it is typically used for an average of 15 days, with an interquartile range of 8 – 17 days. ECMO has become the predominant form of mechanical ventilation in critical cases, with one meta-analysis reporting its use in 98.6% of such patients. It was cleared for COVID use by the FDA in February 2020.

A 2024 study reported that 54% of COVID-19 patients treated with ECMO experienced hemorrhagic complications.[50] Furthermore, despite the use of ECMO, some patients may still require lung transplantation. Figure 12 summarizes ECMO outcome statistics as reported in a 2025 *Journal of Clinical Medicine* paper.[51]

A 2023 study reported mortality rates for ARDS patients with and without ECMO treatment,[52] as summarized in Table 14.

The NIH COVID-19 Treatment Guidelines recommend starting treatment with high-flow nasal cannula oxygen, followed by non-invasive ventilation or intubation, and then progressing to mechanical ventilation. Although ECMO is referenced on 51 pages in the NIH guidelines regarding the use of other therapeutics, there is no explicit discussion or guidance regarding its direct use.

Table 14. Extracorporeal membrane oxygenation (ECMO) impacts on acute respiratory distress syndrome (ARDS) patient mortality

Characteristic	Follow-up	ECMO (%)	Conventional therapy (%)
ARDS-H1N1	6 months	37	53
ARDS	60 days	35	46
ARDS	60 days	34	47
ARDS	90 days	36	48
COVID ARDS	60 days	26	33
COVID ARDS	60 days	35	47

Note: Adopted from Burša *et al.*[51]

8.1.2. Vilobelimab

The monoclonal antibody vilobelimab was initially clinically trialed for septic shock in 2012. A 2022 study reported that all-cause mortality rate of COVID-19 at 28 days was 32% (95% CI: 25 – 39) in the vilobelimab group, compared to 42% (95% CI: 35 – 49) in the placebo group (hazard ratio: 0.73, 95% CI: 0.50 – 1.06; p=0.094).[53] The FDA granted Emergency Use Authorization for vilobelimab on April 04, 2023. The NIH COVID-19 Treatment Guidelines state that, although vilobelimab received a COVID-19 FDA Emergency Use Authorization, there is currently insufficient evidence to recommend either for or against its use in COVID-19.

8.1.3. Other unsuccessful oxygenation treatments

Studies reviewed in "The Mouse That Roared" (R. L. Martin, unpublished report, 2025) reported that other oxygenation treatments were clinically trialed but found to be ineffective. These included the use of hyperbaric chambers along with a cytokine therapeutic (erythropoietin), as well as repurposed drugs such as imatinib (a cancer treatment), methylthioninium chloride, and nebulized recombinant tissue plasminogen activator (commonly used for stroke).

8.2. Cardiovascular system

The cardiovascular system can be compromised by direct viral invasion, hyperinflammation, blood clots, and/or lack of oxygen. This section evaluates the management of blood clots. Well-known anti-coagulants, such as heparin, Xarelto, and aspirin, are employed to prevent or treat

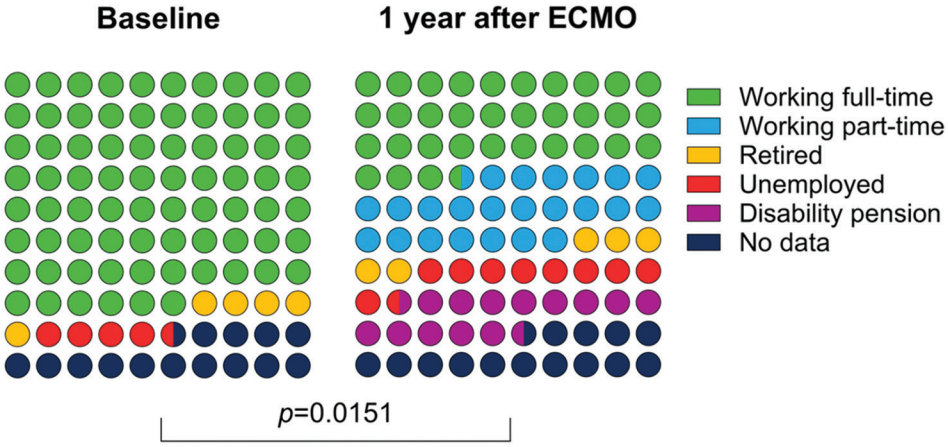


Figure 12. Distribution of extracorporeal membrane oxygenation outcomes. Reprinted from Staudacher *et al.*[50]

thrombosis. However, their use in COVID-19 requires caution, as anticoagulants can significantly increase the risk of bleeding.

In 2021, a study reported that the available evidence did not support the use of therapeutic-dose heparin for thrombosis prevention in critically ill COVID-19 patients.[54] While some benefit was observed in patients with severe comorbidities, the study emphasized the importance of proactive bleeding monitoring, noting that bleeding accounted for 3 – 6% of COVID-19-related deaths.

A 2024 study reported the relative risks and benefits of different heparin doses,[54] as summarized in Table 15.

Heparin received FDA approval for COVID-19-related use on September 17, 2020. The NIH COVID-19 Treatment Guidelines recommend its administration exclusively in hospital settings.

Another approach to mitigate clotting involves dissolving NETs**,** which are networks of extracellular fibers primarily composed of neutrophil DNA. Neutrophils, the immune system's first line of defense, traditionally function by engulfing pathogens and secreting antimicrobials. In 2004, a novel third mechanism was identified: the formation of NETs, which allow neutrophils to trap and kill extracellular pathogens. However, early in the COVID-19 pandemic, NETs were found to exacerbate inflammation and microvascular thrombosis, particularly in ARDS patients' lungs. Several drugs were shown to reduce NET formation, including colchicine, IL-1β blockers, and anakinra. The NIH COVID-19 Treatment Guidelines did not address NETs.

Other anticoagulation approaches discussed in the papers reviewed in "The Mouse that Roared" (R. L. Martin, unpublished report, 2025) lacked sufficient data for a clear assessment of their effectiveness. These included blood vessel dilation, antiplatelet therapies, plasma exchange, caplacizumab, and repurposed drugs used for conditions such as tapeworm (niclosamide), leprosy (clofazimine), multiple myeloma (bortezomib), and hypertension (bosentan). Two renal replacement therapies received FDA Emergency Use Authorization for COVID-19 but were later revoked.

Table 15. Heparin's effectiveness in COVID-19 patients by dosage

Medication effectiveness measures	Therapeutic dose compared to standard dose	Intermediate dose compared to therapeutic dose
VTE[a] risk	1.09 (0.58 – 2.02)	0.85 (0.52 – 1.38)
All-cause mortality	1.12 (0.75 – 1.67)	1.34 (0.83 – 2.17)
Bleeding risk	2.59 (1.87 – 3.57)	2.42 (1.58 – 3.70)

Notes: [a]Venous thromboembolism (VTE) is a condition in which a blood clot forms in a vein. VTE includes deep vein thrombosis (DVT) and pulmonary embolism. DVT occurs when a blood clot forms in a deep vein, usually in the lower leg, thigh, or pelvis. All data presented as odds ratio (95% CI). Table adopted from Chen *et al.*[54]

9. Popular but high-risk therapeutics

Some individuals tried certain therapeutics contrary to medical advice. A few of such therapeutics are listed in Table 16.

10. Future perspective

Presently available antivirals, when administered early and in conjunction with vaccination, have demonstrated considerable effectiveness in reducing the severity and progression of COVID-19. While the emergence of viral variants has rendered all monoclonal antibody therapies ineffective, the Mpro- and RdRp-targeting drugs have, to date, shown resilience to mutation. However, this resistance may not be permanent. Therefore, the proactive development of mutation-resistant antivirals remains a critical area of ongoing research. Notably, a wide range of Mpro-targeting therapeutics have been proposed, some of which claim inherent resistance to mutation and merit further investigation.

10.1. Future direction

Progress could be made by targeting NSPs, particularly NSP1 and the nucleocapsid protein. Inhibiting these proteins can effectively disrupt the virus's life cycle. Importantly, these proteins mutate less frequently than the spike protein.

10.2. Challenges

A major remaining therapeutic challenge in COVID-19 is hyperinflammation. While all approved drugs focus on

Table 16. Popular but high-risk therapeutics against COVID-19

Medication effectiveness measures	ClinicalTrials.gov			Google Scholar	"The Mouse That Roared"
	Total	Completed	Results		
Trump recommended					
Azithromycin	115	42	15	55,200	19
Hydroxychloroquine	237	85	29	64,200	32
Other					
Ivermectin	91	34	14	25,700	40

Note: Statistics from ClinicalTrials.gov, Google Scholar, and "The Mouse That Roared" (R. L. Martin, unpublished report, 2025), as of December 01, 2024.

Table 17. FDA-approved therapeutics against COVID-19

Therapeutics	Descriptions
Prevention	
mRNA vaccines	They are the most important drugs to prevent severe COVID-19 conditions.
Pemgarda	A monoclonal antibody for immunocompromised people. Originally, it showed 84% risk reduction through six months. However, its effectiveness is compromised by viral variants KP. 3.1.1 and XEC.
Suppression of viral replication and inflammation: Antivirals	
Monoclonal antibodies	Approximately 85% mortality reduction early in the COVID-19 pandemic. However, all but Pemgarda were eventually rendered ineffective by emerging variants.
Paxlovid	There are numerous assessments of its impact. One trial reported 89% mortality reduction among unvaccinated patients, in which 80% received Paxlovid and 20% received molnupiravir.
Remdesivir	It is often recommended in combination with another therapeutic and is the NIH's preferred option after Paxlovid. Administration must occur in a hospital setting.
Molnupiravir	It is an excellent alternative for patients who cannot administer Paxlovid.
Suppression of hyperinflammation: Anti-inflammatory agents	
Dexamethasone	None of these treatments is a magic bullet. Dexamethasone remains the most frequently used, followed by baricitinib. Recommendations for their use are quite complex, and remdesivir is often recommended alongside them.
Anakinra	
Baricitinib	
Tocilizumab	
Suppression of organ damage: Hypoxia	
ECMO	After other less aggressive oxygenation approaches have been attempted, ECMO is used. Early initiation of ECMO results in a 36% mortality rate compared to 58.9% with late initiation. Among patients receiving prolonged mechanical ventilation, one-year and five-year survival rates are 24.3% and 14.6%, respectively.
Vilobelimab	It is a monoclonal antibody that reduced 28-day mortality to 31.7%, compared to 41.6% in the placebo group.
Suppression of organ damage: Cardiovascular clotting	
Heparin	It must be used with extreme caution due to the risk of bleeding.

Abbreviations: ECMO: Extracorporeal membrane oxygenation; mRNA: Messenger RNA; NIH: National Institutes of Health.

mitigating its effects, none directly address its root causes. Moving forward, three promising strategies merit focused research and development:

(i) Prevent the dysregulation of the renin-angiotensin system
(ii) Protect the innate immune system from disruption by viral structural and NSPs
(iii) Target and inhibit highly inflammatory cytokines, particularly IL-6.

10.3. "Shoot for the Moon" program

Finally, a high-payoff strategy would be the development of antivirals targeting conserved regions of viruses, those that are stable across mutations and invariant among related coronaviruses. Furthermore, if such an antiviral completes the rigorous Phase 3 approval process for COVID-19, it may only require a Phase 2 trial for a related virus.

A proposed "Shoot for the Moon" program would support ambitious, long-range research aimed at developing broad-spectrum, pan-virus antivirals, especially against the most dangerous viral families, such as those that include Ebola and Marburg.

11. Conclusion

Even though there were 4,855 FDA-registered COVID-19 clinical trials through October 2024, no new therapeutics received FDA or EU approval during the pandemic. Fortunately, the pre-existing arsenal of therapeutics has proven effective, particularly when deployed early in the course of the disease. Table 17 summarizes all FDA-approved or FDA-cleared (in the case of ECMO) COVID-19 therapeutics.

Although the NIH is silent on the following promising therapeutics, they merit consideration. They have demonstrated positive impacts with minimal or no downsides, making them, in effect, Pascal's Wagers. These therapeutics are:

(i) Iodine nasal spray or gargle: Use before and after high-risk exposures.
(ii) Metformin: It also shows promise in cancer prevention.

(iii) Probiotics: While the evidence is less robust, they support gut health and may aid immune function with little risk involved.

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