Identification and Development of Prophylactics and Therapeutics for COVID-19

This manuscript ([permalink](https://greenelab.github.io/covid19-review/v/59a3356e20e03c5dfb497cc2bfe11ce55b7f1a02/)) was automatically generated from [greenelab/covid19-review@59a3356](https://github.com/greenelab/covid19-review/tree/59a3356e20e03c5dfb497cc2bfe11ce55b7f1a02) on February 14, 2021. It represents one section of a larger evolving review on SARS-CoV-2 and COVID-19 available at <https://greenelab.github.io/covid19-review/>

**This in progress manuscript is not intended for the general public.** This is a review paper that is authored by scientists for an audience of scientists to discuss research that is in progress. If you are interested in guidelines on testing, therapies, or other issues related to your health, you should not use this document. Instead, you should collect information from your local health department, the [CDC’s guidance](https://www.cdc.gov/coronavirus/2019-ncov/index.html), or your own government.

# Authors

* **Halie M. Rando** [0000-0001-7688-1770](https://orcid.org/0000-0001-7688-1770) [rando2](https://github.com/rando2) [tamefoxtime](https://twitter.com/tamefoxtime) Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America; Department of Biochemistry and Molecular Genetics, University of Colorado School of Medicine, Aurora, Colorado, United States of America; Center for Health AI, University of Colorado School of Medicine, Aurora, Colorado, United States of America · Funded by the Gordon and Betty Moore Foundation (GBMF 4552)
* **Nils Wellhausen** [0000-0001-8955-7582](https://orcid.org/0000-0001-8955-7582) [nilswellhausen](https://github.com/nilswellhausen) Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America
* **Soumita Ghosh** [0000-0002-2783-2750](https://orcid.org/0000-0002-2783-2750) [soumitagh](https://github.com/soumitagh) Institute of Translational Medicine and Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America
* **Anna Ada Dattoli** [0000-0003-1462-831X](https://orcid.org/0000-0003-1462-831X) [aadattoli](https://github.com/aadattoli) [aadattoli](https://twitter.com/aadattoli) Department of Systems Pharmacology & Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
* **Fengling Hu** [0000-0003-1081-5038](https://orcid.org/0000-0003-1081-5038) [hufengling](https://github.com/hufengling) [hufengling](https://twitter.com/hufengling) Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America
* **Alexandra J. Lee** [0000-0002-0208-3730](https://orcid.org/0000-0002-0208-3730) [ajlee21](https://github.com/ajlee21) Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America · Funded by the Gordon and Betty Moore Foundation (GBMF 4552)
* **Diane N. Rafizadeh** [0000-0002-2838-067X](https://orcid.org/0000-0002-2838-067X) [dianerafi](https://github.com/dianerafi) Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America; Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America · Funded by NIH Medical Scientist Training Program T32 GM07170
* **James Brian Byrd** [0000-0002-0509-3520](https://orcid.org/0000-0002-0509-3520) [byrdjb](https://github.com/byrdjb) [thebyrdlab](https://twitter.com/thebyrdlab) University of Michigan School of Medicine, Ann Arbor, Michigan, United States of America · Funded by NIH K23HL128909; FastGrants
* **Yanjun Qi** [0000-0002-5796-7453](https://orcid.org/0000-0002-5796-7453) [qiyanjun](https://github.com/qiyanjun) Department of Computer Science, University of Virginia, Charlottesville, VA, United States of America
* **Yuchen Sun** [kevinsunofficial](https://github.com/kevinsunofficial) Department of Computer Science, University of Virginia, Charlottesville, VA, United States of America
* **Jeffrey M. Field** [0000-0001-7161-7284](https://orcid.org/0000-0001-7161-7284) [Jeff-Field](https://github.com/Jeff-Field) Department of Pharmacology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
* **Marouen Ben Guebila** [0000-0001-5934-966X](https://orcid.org/0000-0001-5934-966X) [marouenbg](https://github.com/marouenbg) [marouenbg](https://twitter.com/marouenbg) Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, United States of America
* **Nafisa M. Jadavji** [0000-0002-3557-7307](https://orcid.org/0000-0002-3557-7307) [nafisajadavji](https://github.com/nafisajadavji) [nafisajadavji](https://twitter.com/nafisajadavji) Biomedical Science, Midwestern University, Glendale, AZ, United States of America; Department of Neuroscience, Carleton University, Ottawa, Ontario, Canada · Funded by the American Heart Association (20AIREA35050015)
* **Ronan Lordan** [0000-0001-9668-3368](https://orcid.org/0000-0001-9668-3368) [RLordan](https://github.com/RLordan) [el\_ronan](https://twitter.com/el_ronan) Institute for Translational Medicine and Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104-5158, USA
* **Ashwin N. Skelly** [0000-0002-1565-3376](https://orcid.org/0000-0002-1565-3376) [anskelly](https://github.com/anskelly) Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America; Institute for Immunology, University of Pennsylvania Perelman School of Medicine, Philadelphia, United States of America · Funded by NIH Medical Scientist Training Program T32 GM07170
* **Christian Brueffer** [0000-0002-3826-0989](https://orcid.org/0000-0002-3826-0989) [cbrueffer](https://github.com/cbrueffer) [cbrueffer](https://twitter.com/cbrueffer) Department of Clinical Sciences, Lund University, Lund, Sweden
* **Jinhui Wang** [0000-0002-5796-8130](https://orcid.org/0000-0002-5796-8130) [jinhui2](https://github.com/jinhui2) Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America
* **Rishi Raj Goel** [https://orcid.org/0000-0003-1715-5191](https://orcid.org/https://orcid.org/0000-0003-1715-5191) [rishirajgoel](https://github.com/rishirajgoel) [rishirajgoel](https://twitter.com/rishirajgoel) Institute for Immunology, University of Pennsylvania, Philadelphia, PA, United States of America
* **YoSon Park** [0000-0002-0465-4744](https://orcid.org/0000-0002-0465-4744) [ypar](https://github.com/ypar) [**yoson**](https://twitter.com/__yoson__) Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America · Funded by NHGRI R01 HG10067
* **COVID-19 Review Consortium**
* **Simina M. Boca** [0000-0002-1400-3398](https://orcid.org/0000-0002-1400-3398) [SiminaB](https://github.com/SiminaB) Innovation Center for Biomedical Informatics, Georgetown University Medical Center, Washington, District of Columbia, United States of America
* **Anthony Gitter** [0000-0002-5324-9833](https://orcid.org/0000-0002-5324-9833) [agitter](https://github.com/agitter) [anthonygitter](https://twitter.com/anthonygitter) Department of Biostatistics and Medical Informatics, University of Wisconsin-Madison, Madison, Wisconsin, United States of America; Morgridge Institute for Research, Madison, Wisconsin, United States of America · Funded by John W. and Jeanne M. Rowe Center for Research in Virology
* **Casey S. Greene** [0000-0001-8713-9213](https://orcid.org/0000-0001-8713-9213) [cgreene](https://github.com/cgreene) [GreeneScientist](https://twitter.com/GreeneScientist) Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America; Childhood Cancer Data Lab, Alex’s Lemonade Stand Foundation, Philadelphia, Pennsylvania, United States of America; Department of Biochemistry and Molecular Genetics, University of Colorado School of Medicine, Aurora, Colorado, United States of America; Center for Health AI, University of Colorado School of Medicine, Aurora, Colorado, United States of America · Funded by the Gordon and Betty Moore Foundation (GBMF 4552); the National Human Genome Research Institute (R01 HG010067)

**COVID-19 Review Consortium:** Vikas Bansal, John P. Barton, Simina M. Boca, Christian Brueffer, James Brian Byrd, Stephen Capone, Shikta Das, Anna Ada Dattoli, John J. Dziak, Jeffrey M. Field, Soumita Ghosh, Anthony Gitter, Rishi Raj Goel, Casey S. Greene, Marouen Ben Guebila, Fengling Hu, Nafisa M. Jadavji, Sergey Knyazev, Likhitha Kolla, Alexandra J. Lee, Ronan Lordan, Tiago Lubiana, Temitayo Lukan, Adam L. MacLean, David Mai, Serghei Mangul, David Manheim, Lucy D'Agostino McGowan, YoSon Park, Dimitri Perrin, Yanjun Qi, Diane N. Rafizadeh, Bharath Ramsundar, Halie M. Rando, Sandipan Ray, Michael P. Robson, Elizabeth Sell, Lamonica Shinholster, Ashwin N. Skelly, Yuchen Sun, Gregory L Szeto, Ryan Velazquez, Jinhui Wang, Nils Wellhausen

Authors with similar contributions are ordered alphabetically.

## Abstract

After emerging in China in late 2019, the novel coronavirus SARS-CoV-2 spread worldwide and as of early 2021, continues to significantly impact most countries. Only a small number of coronaviruses are known to infect humans, and only two are associated with the severe outcomes associated with SARS-CoV-2: SARS-CoV-1, a closely related species of SARS-CoV-2 that emerged in 2002, and MERS-CoV, which emerged in 2012. Both of these previous epidemics were controlled fairly rapidly through public health measures, and no vaccines or robust therapeutic interventions were identified. However, previous insights into the immune response to coronaviruses gained during the outbreaks of SARS and MERS have proved beneficial to identifying approaches to the treatment and prophylaxis of COVID-19. A number of potential therapeutics against SARS-CoV-2 were rapidly identified, leading to a large number of clinical trials investigating a variety of possible therapeutic approaches being initiated early on in the pandemic. As a result, a small number of therapeutics have already been authorized by regulatory agencies such as the Food and Drug Administration (FDA) in the United States, and many other therapeutics remain under investigation. Here, we describe a range of approaches for the treatment of COVID-19, along with their proposed mechanisms of action and the current status of clinical investigation into each candidate. The status of these investigations will continue to evolve, and this review will be updated as progress is made.

## Importance

The COVID-19 pandemic is a rapidly evolving crisis. With the worldwide scientific community shifting focus onto the SARS-CoV-2 virus and the disease it causes, a large number of possible pharmaceutical approaches for treatment and prevention have been proposed. What is known about each of these potential interventions evolved rapidly throughout 2020 and early 2021. In March 2020, we began monitoring a range of candidates and have continued to update this manuscript as new information has become available. Some therapeutics have been supported, others have been revealed to be unlikely to confer any therapeutic benefits, and most require more data before a conclusion can be drawn. This rapidly changing area of research provides important insight into how the ongoing pandemic can be managed and also demonstrates the power of interdisciplinary collaboration to rapidly understand a virus and match its characteristics with existing or novel pharmaceuticals.

## Introduction

The novel coronavirus *Severe acute respiratory syndrome-related coronavirus 2* (SARS-CoV-2) emerged in late 2019 and quickly precipitated the worldwide spread of novel coronavirus disease 2019 (COVID-19). COVID-19 is associated with symptoms ranging from none (asymptomatic) to mild to severe, with approximately 2% of patients dying from COVID-19-related complications, such as acute respiratory disease syndrome (ARDS) [[1](#ref-r366f5T3)]. The virus is likely spread between people primarily by droplets, with the role of contact and aerosol transmission still in question [[2](#ref-82XnTbtX),[3](#ref-cw5j7x80)]. As a result, public health guidelines have been critical to efforts to control the spread of the virus. However, as of early 2021, COVID-19 remains a significant worldwide concern (Figure [1](#fig:csse-deaths)), with cases in some places surging far above the numbers reported during the initial outbreak in early 2020. Due to the continued threat of the virus and the severity of the disease, the identification and development of prophylactic and therapeutic interventions have emerged as significant international priorities. Both approaches hold valuable potential for controlling the impact of the disease. Prophylactics bolster immunity to prevent an individual from contracting a disease, whereas therapeutics treat a disease in individuals who have already been infected. While vaccine development programs have attracted significant attention and produced a number of promising candidates, there is also an immediate need for treatments that palliate symptoms and prevent the most severe outcomes from infection. Fortunately, prior developments during other recent pandemics, especially those caused by human coronaviruses (HCoV), have provided a number of hypotheses guiding a biomedical approach to the novel coronavirus infection.

2,393,751 COVID-19 deaths had been reported worldwide as of February 13, 2021 (Figure [1](#fig:csse-deaths)).

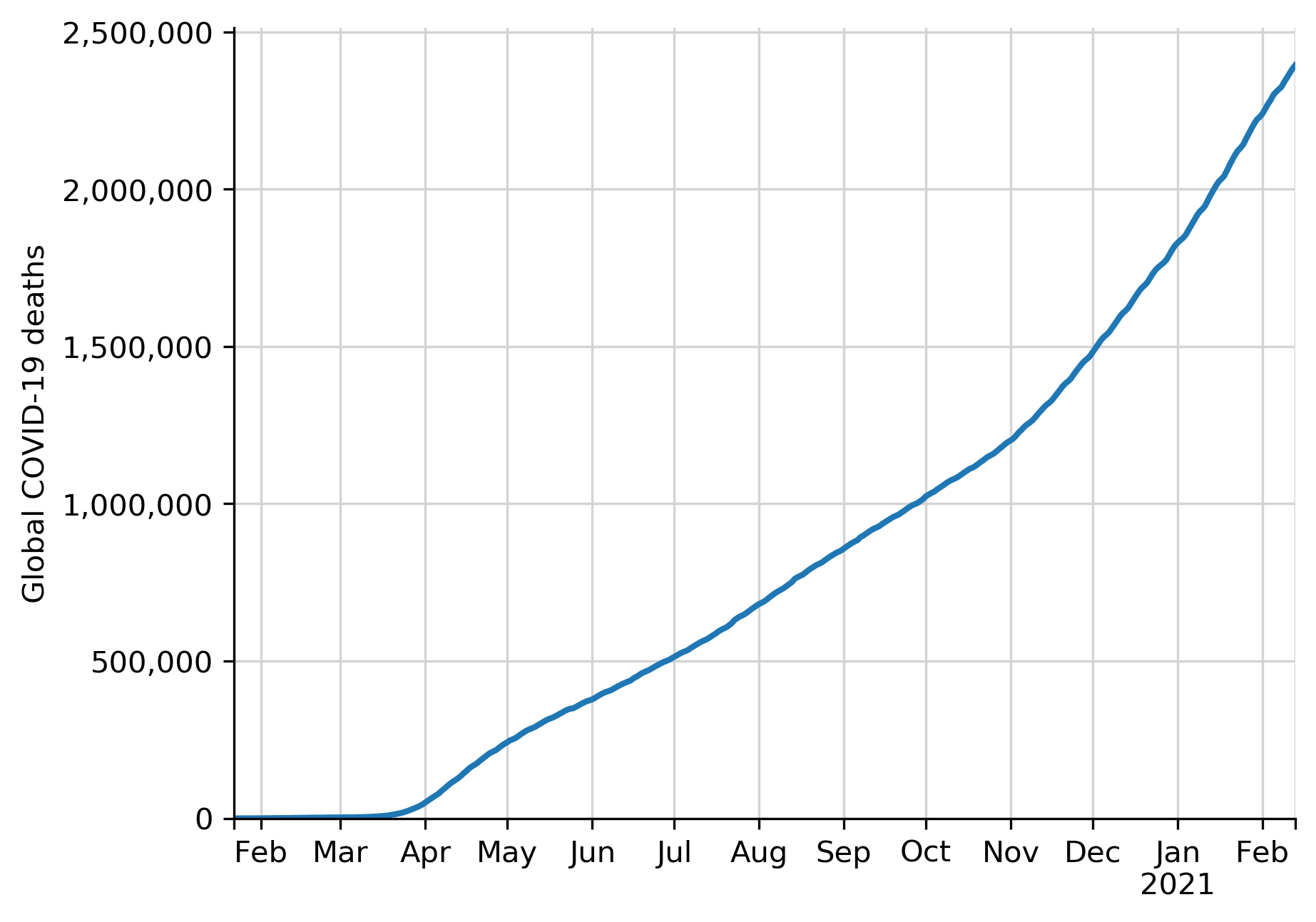


Figure 1: **Cumulative global COVID-19 deaths since January 22, 2020.** Data are from the COVID-19 Data Repository by the Center for Systems Science and Engineering at Johns Hopkins University [[4](#ref-MrwDDw9R)].

### Lessons from Prior HCoV Outbreaks

SARS-CoV-2’s rapid shift from an unknown virus to a significant worldwide threat closely parallels the emergence of *Severe acute respiratory syndrome-related coronavirus* (SARS-CoV-1). The first documented case of COVID-19 was reported in Wuhan, China in November 2019, and the disease quickly spread worldwide during the early months of 2020. Similarly, the first case of SARS was reported in November 2002 in the Guangdong Province of China, and it spread within China and then into several countries across continents over the following months [[5](#ref-sP4wQEiM),[6](#ref-G5NJrE75)]. In fact, genome sequencing quickly revealed the virus causing COVID-19 to be a novel betacoronavirus closely related to SARS-CoV-1 [[7](#ref-Bp847Lfa)].

There are many similarities but also some differences in the characteristics of the two viruses that determine how they spread. SARS infection is severe, with an estimated death rate of 9.5% [[5](#ref-sP4wQEiM)], while estimates of the death rate associated with COVID-19 are much lower, at approximately 2% [[1](#ref-r366f5T3)]. SARS-CoV-1 is highly contagious via droplet transmission and has a basic reproduction number (R0) of 4 (i.e., each person infected was estimated to infect four other people) [[5](#ref-sP4wQEiM)]. SARS-CoV-2 also appears to be spread primarily by droplet transmission [[2](#ref-82XnTbtX),[3](#ref-cw5j7x80)], and most estimates of its R0 fall between 2.5 and 3 [[1](#ref-r366f5T3)]. Furthermore, the 17-year difference in the timing of these two outbreaks has led to some major differences in the tools available for the international community’s response. At the time that SARS-CoV-1 emerged, no new HCoV had been identified in almost 40 years [[6](#ref-G5NJrE75)]. The identity of the virus underlying the SARS disease remained unknown until April of 2003, when the SARS-CoV-1 virus was characterized through a worldwide scientific effort spearheaded by the World Health Organization (WHO) [[6](#ref-G5NJrE75)]. In contrast, the SARS-CoV-2 genomic sequence was released on January 3, 2020 [[7](#ref-Bp847Lfa)], only days after the international community became aware of the novel pneumonia-like illness now known as COVID-19. While SARS-CoV-1 belonged to a distinct lineage from the two other HCoV known at the time of its discovery [[5](#ref-sP4wQEiM)], SARS-CoV-2 is closely related to SARS-CoV-1 and a more distant relative of another HCoV characterized in 2012, *Middle East respiratory syndrome-related coronavirus* [[8](#ref-1Fqilxaum),[9](#ref-7Ee6Sz9l)].

Despite their phylogenetic similarity, SARS-CoV-2 emerged under very different circumstances than SARS-CoV-1 in terms of scientific knowledge about HCoV. The trajectories of the pandemics associated with each of the viruses have also diverged significantly. By July 2003, the SARS outbreak was officially determined to be under control, with the success credited to infection management practices such as mask wearing [[6](#ref-G5NJrE75)]. In contrast, MERS is still circulating and remains a concern; although the fatality rate is very high at almost 35%, the disease is much less easily transmitted, as its R0 has been estimated to be 1 [[5](#ref-sP4wQEiM)]. The low R0 in combination with public health practices allowed for its spread to be contained [[5](#ref-sP4wQEiM)]. Neither of these trajectories are comparable to that of SARS-CoV-2, which remains a serious threat worldwide more than a year after the first cases of COVID-19 emerged.

Early results suggest that pharmaceutical interventions for COVID-19 may be more successful than efforts to develop prophylactics and therapeutics for SARS and MERS were. Care for SARS and MERS patients prioritized supportive care and symptom management [[5](#ref-sP4wQEiM)]. To the extent that clinical treatments for SARS and MERS were explored, there is generally a lack of evidence supporting their efficacy. For example, Ribavirin is an antiviral that was often used in combination with corticosteroids and sometimes interferon (IFN) medications to treat SARS and MERS [[6](#ref-G5NJrE75)], but its effects have been found to be inconclusive in retrospective and *in vitro* analyses of SARS and the SARS-CoV-1 virus, respectively [[6](#ref-G5NJrE75)]. IFNs and Ribavirin have shown promise in *in vitro* analyses of MERS, but their clinical effectiveness remains unknown [[6](#ref-G5NJrE75)]. Therefore, only limited pharmaceutical advances from prior HCoV outbreaks can be adopted to COVID-19. Importantly, though, prior analyses of the virological and pathogenic properties of SARS-CoV-1 and MERS-CoV provide a strong foundation for the development of hypotheses about SARS-CoV-2 that have served to accelerated the development and identification of potential prophylactic and therapeutic approaches.

### Therapeutic Approaches

Therapeutic approaches to the current pandemic can utilize two potential avenues: they can reduce the symptoms that are harmful to COVID-19 patients, or they can directly target the virus to hinder the spread of infection. The goal of the former is to reduce the severity and risks of an active infection, while for the latter, it is to inhibit the replication of the virus once an individual is infected. A variety of symptom profiles with a range of severity are associated with COVID-19, many of which are not life-threatening. A study of COVID-19 patients in a hospital in Berlin, Germany found that the symptoms associated with the highest risk of death included infection-related symptoms, such as sepsis, respiratory symptoms such as ARDS, and cardiovascular failure or pulmonary embolism [[10](#ref-xnPm1mx8)]. Therapeutics that reduce the risks associated with these severe outcomes hold particular potential to reduce the pandemic death toll. On the other hand, therapeutics that directly target the virus itself would hold the potential to prevent people infected with SARS-CoV-2 from developing potentially damaging symptoms. These treatments typically fall into the broad category of antivirals. Antiviral therapies hinder the spread of a virus within the host, rather than destroying existing copies of the virus, and these drugs can vary in their specificity to a narrow or broad range of viral targets. For both categories, uncertainty often surrounds the treatments’ exact mechanisms of action, as most therapies have secondary or off-target effects.

A large number of clinical trials investigating a range of possible therapeutics and prophylactics for COVID-19 are currently in progress or have already been completed (Figure [2](#fig:ebm-trials)). The purpose of this review is to critically appraise the literature surrounding a subset of clinical trials and to evaluate a range of approaches to repurpose existing or develop novel approaches to the prevention, mitigation, and treatment of coronavirus infections. The treatments and prophylactics evaluated here are classified according to their biological properties, specifically whether they are biologics (produced from components of organisms) or small molecules. Small molecule drugs include drugs targeted at viral particles, drugs targeted at host proteins, and broad spectrum pharmaceuticals, while biologics include antibodies and interferons. As results become available from additional clinical trials, we will continue to update this manuscript to keep pace with the current understanding of which therapeutics may be effective against SARS-CoV-2 or for COVID-19.

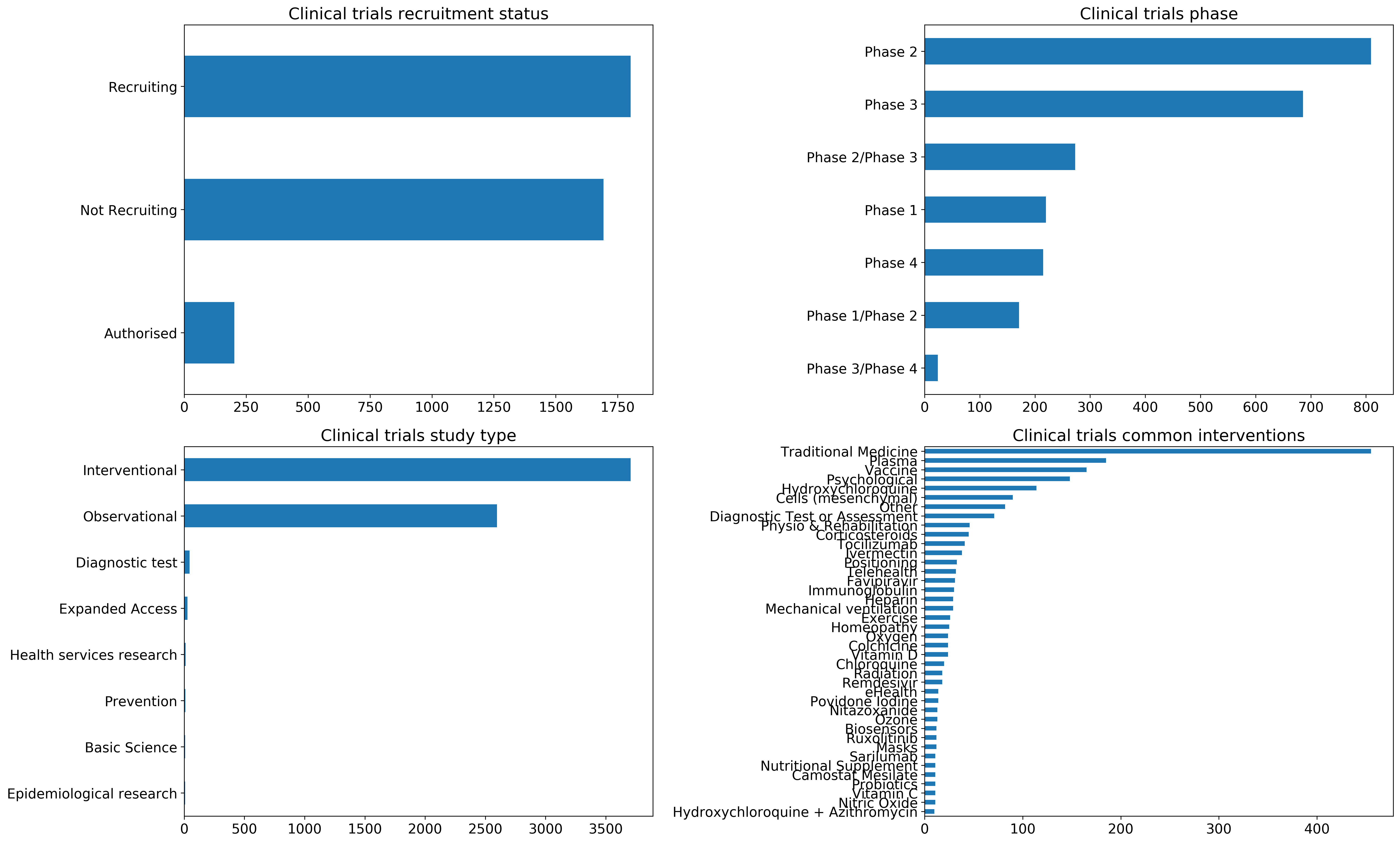


Figure 2: **COVID-19 clinical trials.** There are 6,417 COVID-19 clinical trials of which 3,706 are interventional. The study types include only types used in at least five trials. Interventional trials only are analyzed in the figures depicting status, phase, and intervention. Of the interventional trials, 98 trials had reported results as of November 9, 2020. Recruitment status and trial phase are shown only for interventional trials in which the status or phase is recorded. The common interventions are all interventions used in at least ten trials. Combinations of interventions, such as Hydroxychloroquine + Azithromycin, are tallied separately from the individual interventions. Trials data are from the University of Oxford Evidence-Based Medicine Data Lab’s COVID-19 TrialsTracker [[11](#ref-SSbnPnzT)].

## Small Molecule Drugs

Small molecules are synthesized compounds of low molecular weight, typically less than 1 kilodalton (kDa) [[12](#ref-CcEjS89m)]. Small-molecule pharmaceutical agents have been a backbone of drug development since the discovery of penicillin in the early twentieth century [[13](#ref-ZtfLQJhh)]. It and other antibiotics have long been among the best known applications of small molecules to therapeutics, but biotechnological developments such as the prediction of protein-protein interactions have facilitated advances in precise targeting of specific structures using small molecules [[13](#ref-ZtfLQJhh)]. Small molecule drugs today encompass a wide range of therapeutics beyond antibiotics, including antivirals, protein inhibitors, and many broad-spectrum pharmaceuticals.

### Small Molecule Antivirals

Antiviral drugs against SARS-CoV-2 are designed to inhibit replication of a virus within an epithelial host cell. This process requires inhibiting the replication cycle of a virus by disrupting one of six fundamental steps [[14](#ref-14gthSuhm)]. In the first of these steps, the virus attaches to and enters the host cell through endocytosis. Then the virus undergoes uncoating, which is classically defined as the release of viral contents into the host cell. Next, the viral genetic material enters the nucleus where it gets replicated during the biosynthesis stage. During the assembly stage, viral proteins are translated, allowing new viral particles to be assembled. In the final step new viruses are released into the extracellular environment. Many antiviral drugs are designed to inhibit the replication of viral genetic material during the biosynthesis step. Unlike DNA viruses, which can use the host enzymes to propagate themselves, RNA viruses like SARS-CoV-2 depend on their own polymerase, the RNA-dependent RNA polymerase (RdRP), for replication [[15](#ref-tn6j6IZ0),[16](#ref-Sh1FwWps)]. Targeting RdRP is therefore an effective strategy for antivirals against RNA viruses and is the proposed mechanism underlying the treatment of SARS and MERS with Ribavirin [[17](#ref-6Qlsbuqr)]. However, although antivirals are designed to target a virus, they can also impact other processes in the host and may have unintended effects. Therefore, these therapeutics must be evaluated for both efficacy and safety.

#### Nucleoside and Nucleotide Analogs

##### Favipiravir

Favipiravir (Avigan), also known as T-705, was discovered by Toyama Chemical Co., Ltd. [[18](#ref-IkAU62Pd)]. The drug was found to be effective at blocking viral amplification in several influenza subtypes as well as other RNA viruses, such as *Flaviviridae* and *Picornaviridae*, through a reduction in plaque formation [[19](#ref-EgoJKtW4)] and viral replication in Madin-Darby canine kidney cells [[20](#ref-rG5RCRdJ)]. Furthermore, inoculation of mice with favipiravir was shown to increase survival of influenza infections [[19](#ref-EgoJKtW4),[20](#ref-rG5RCRdJ)]. In 2014, the drug was approved in Japan for the treatment of influenza that was resistant to conventional treatments like neuraminidase inhibitors [[21](#ref-14p3btkRH)]. Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) acts as a purine and purine nucleoside analogue that inhibits viral RNA polymerase in a dose-dependent manner across a range of RNA viruses, including influenza viruses [[22](#ref-DpdKJbki),[23](#ref-9j7NVPJS),[24](#ref-IYEoCGHy),[25](#ref-7d1TnpE3),[26](#ref-15kQ4QYbx)]. Nucleotides and nucleosides are the natural building blocks for RNA synthesis. Because of this, modifications to nucleotides and nucleosides can disrupt key processes including replication [[27](#ref-MPJdSF1p)]. Biochemical experiments showed that favipiravir was recognized as a purine nucleoside analogue and incorporated into the viral RNA template. A single incorporation does not influence RNA transcription; however, multiple events of incorporation lead to the arrest of RNA synthesis [[28](#ref-ukZRKllk)]. Evidence for T-705 inhibiting viral RNA polymerase are based on time-of-drug addition studies that found that viral loads were reduced with the addition of favipiravir in early times post-infection [[22](#ref-DpdKJbki),[25](#ref-7d1TnpE3),[26](#ref-15kQ4QYbx)].

The effectiveness of favipiravir for treating patients with COVID-19 is currently under investigation. An open-label, nonrandomized, before-after controlled study was recently conducted [[29](#ref-13Oz7yRPx)]. The study included 80 COVID-19 patients (35 treated with favipiravir, 45 control) from the isolation ward of the National Clinical Research Center for Infectious Diseases (The Third People’s Hospital of Shenzhen), Shenzhen, China. The patients in the control group were treated with other antivirals, such as lopinavir and ritonavir. It should be noted that although the control patients received antivirals, two subsequent large-scale analyses, the WHO Solidarity trial and the RECOVERY trial, identified no effect of lopinavir or of a lopinavir-ritonavir combination, respectively, on the metrics of COVID-19-related mortality that each assessed [[30](#ref-jShm9uhy),[31](#ref-fTWlYlvp),[32](#ref-xM0IhxIr)]. Treatment was applied on days 2-14; treatment stopped either when viral clearance was confirmed or at day 14. The efficacy of the treatment was measured by, first, the time until viral clearance using Kaplan-Meier survival curves, and, second, the improvement rate of chest computed tomography (CT) scans on day 14 after treatment. The study found that favipiravir increased the speed of recovery, measured as viral clearance from the patient by RT-PCR, with patients receiving favipiravir recovering in four days compared to 11 days for patients receiving antivirals such as lopinavir and ritonavir. Additionally, the lung CT scans of patients treated with favipiravir showed significantly higher improvement rates (91%) on day 14 compared to control patients (62%). However, there were adverse side effects in 4 (11%) favipiravir-treated patients and 25 (56%) control patients. The adverse side effects included diarrhea, vomiting, nausea, rash, and liver and kidney injury. Overall, despite the study reporting clinical improvement in favipiravir-treated patients, due to some issues with study design, it cannot be determined whether treatment with favipiravir had an effect or whether these patients would have recovered regardless of any treatment. For example, despite the significant differences observed between the two treatment groups, follow-up analysis is necessary due to the small sample size. The selection of patients did not take into consideration important factors such as previous clinical conditions or sex, and there was no age categorization. The study was neither randomized nor blinded, and the baseline control group was another antiviral instead of a placebo. Additionally, it should be noted that this study was temporarily retracted and then restored without an explanation [[33](#ref-hfAF6aDr)].

In late 2020 and early 2021, the first randomized controlled trials of favipiravir for the treatment of COVID-19 released results [[34](#ref-APU0cUZz),[35](#ref-15rGJX7Hl),[36](#ref-32n9UEkQ)]. The first [[34](#ref-APU0cUZz)] used a randomized, controlled, open-label design to compare two drugs, favipiravir and baloxavir marboxil, to standard of care (SOC) alone. Here, SOC included antivirals such as lopinavir/ritonavir and was administered to all patients. The primary endpoint analyzed was viral clearance at day 14. The sample size for this study was very small, with 29 total patients enrolled, and no significant effect of the treatments was found for the primary or any of the secondary outcomes analyzed, which included mortality. The second study was larger, with 96 patients enrolled, and also utilized a randomized design. This study enrolled only patients with mild to moderate symptoms and randomized them into two groups: one receiving chloroquine (CQ) in addition to SOC, and the other receiving favipiravir in addition to SOC. This study reported a non-significant trend for patients receiving favipiravir to have a shorter hospital stay and less likelihood of progressing to mechanical ventilation or to an oxygen saturation < 90%. However, given the fact that favipiravir was being compared to CQ, which is now widely understood to be ineffective for treating COVID-19, these results do not suggest that favipiravir was likely to have had a strong effect on these outcomes. On the other hand, another trial of 60 patients reported a significant effect of favipiravir on viral clearance at four days (a secondary endpoint), but not at 10 days (the primary endpoint) [[36](#ref-32n9UEkQ)]. This study, as well as a prior study of favipiravir [[37](#ref-qwlYY6jn)], also reported that the drug was generally well-tolerated. Thus, in combination, these small studies suggest that the effects of favipiravir as a treatment for COVID-19 cannot be determined based on the available evidence, but additionally, none raise major concerns about the safety profile of the drug.

##### Remdesivir

Remdesivir (GS-5734) is an intravenous antiviral that was developed by Gilead Sciences to treat Ebola Virus Disease (EVD). At the outset of the COVID-19 pandemic, it did not have any have any FDA-approved use. However, on May 1, 2020, the FDA issued an Emergency Use Authorization (EUA) for remdesivir for the treatment of hospitalized COVID-19 patients [[38](#ref-1BYoe0y2H)]. The EUA was based on information from two clinical trials, NCT04280705 and NCT04292899 [[39](#ref-yTCAmOyt),[40](#ref-1ATTPbCCO),[41](#ref-DtpdBrgt),[42](#ref-16zLDIOyk)]. Remdesivir is metabolized to GS-441524, an adenosine analog that inhibits a broad range of polymerases and then evades exonuclease repair, causing chain termination [[43](#ref-YaxKcqq8),[44](#ref-lIko9Imd),[45](#ref-IhdcvbzC)]. A clinical trial in the Democratic Republic of Congo found some evidence of effectiveness against EVD, but two antibody preparations were found to be more effective, and remdesivir was not pursued [[46](#ref-gnfviuGp)]. Although it was developed against EVD, remdesivir also inhibits polymerase and replication of the coronaviruses MERS-CoV and SARS-CoV-1 in cell culture assays with submicromolar IC50s [[47](#ref-1H0NPTMw9)]. It has also been found to inhibit SARS-CoV-2, showing synergy with CQ *in vitro* [[45](#ref-IhdcvbzC)].

Remdesivir was first used on some COVID-19 patients under compassionate use guidelines [[48](#ref-D4HwvRMd),[49](#ref-zoLViMNg)]. All were in late stages of COVID-19 infection, and initial reports were inconclusive about the drug’s efficacy. Gilead Sciences, the maker of remdesivir, led a recent publication that reported outcomes for compassionate use of the drug in 61 patients hospitalized with confirmed COVID-19. Here, 200 mg of remdesivir was administered intravenously on day 1, followed by a further 100 mg/day for 9 days [[42](#ref-16zLDIOyk)]. There were significant issues with the study design, or lack thereof. There was no randomized control group. The inclusion criteria were variable: some patients only required low doses of oxygen, while others required ventilation. The study included many sites, potentially with variable inclusion criteria and treatment protocols. The patients analyzed had mixed demographics. There was a short follow-up period of investigation. Some patients worsened, some patients died, and eight were excluded from the analysis mainly due to missing post-baseline information; thus, their health was unaccounted for. Therefore, even though the study reported clinical improvement in 68% of the 53 patients ultimately evaluated, due to the significant issues with study design, it could not be determined whether treatment with remdesivir had an effect or whether these patients would have recovered regardless of treatment. Another study comparing 5- and 10-day treatment regimens reported similar results but was also limited because of the lack of a placebo control [[51](#ref-w5y1LWUR)]. These studies did not alter the understanding of the efficacy of remdesivir in treating COVID-19, but the encouraging results provided motivation for placebo-controlled studies.

Remdesivir was later tested in a double-blind placebo-controlled phase 3 clinical trial performed at 60 trial sites, 45 of which were in the United States [[40](#ref-1ATTPbCCO),[41](#ref-DtpdBrgt)]. The trial recruited 1,062 patients and randomly assigned them to placebo treatment or treatment with remdesivir. Patients were stratified for randomization based on site and the severity of disease presentation at baseline [[41](#ref-DtpdBrgt)]. The treatment was 200 mg on day 1, followed by 100 mg on days 2 through 10. Data was analyzed from a total of 1,059 patients who completed the 29-day course of the trial, with 517 assigned to remdesivir and 508 to placebo [[41](#ref-DtpdBrgt)]. The two groups were well matched demographically and clinically at baseline. Those who received remdesivir had a median recovery time of 10 days, as compared with 15 days in those who received placebo (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; *p* < 0.001). The Kaplan-Meier estimates of mortality by 14 days were 6.7% with remdesivir and 11.9% with placebo, with a hazard ratio (HR) for death of 0.55 and a 95% CI of 0.36 to 0.83, and at day 29, remdesivir corresponded to 11.4% and the placebo to 15.2% (HR: 0.73; 95% CI: 0.52 to 1.03). Serious adverse events were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients in the placebo group (31.6%). This study also reported an association between remdesivir administration and both clinical improvement and a lack of progression to more invasive respiratory intervention in patients receiving non-invasive and invasive ventilation at randomization [[41](#ref-DtpdBrgt)]. Largely on the results of this trial, the FDA reissued and expanded the EUA for remdesivir for the treatment of hospitalized COVID-19 patients ages twelve and older [[38](#ref-1BYoe0y2H)]. Additional clinical trials [[45](#ref-IhdcvbzC),[52](#ref-oso9r21L),[53](#ref-1q4PmqTm),[54](#ref-rUTsIlZs),[55](#ref-JSoOOX98)] are currently underway to evaluate the use of remdesivir to treat COVID-19 patients at both early and late stages of infection and in combination with other drugs (Figure [2](#fig:ebm-trials)). As of October 22, 2020, remdesivir received FDA approval based on three clinical trials [[56](#ref-1DTFVDWTn)].

However, results suggesting no effect of remdesivir on survival were reported by the WHO Solidarity trial [[30](#ref-jShm9uhy)]. This large-scale, open-label trial enrolled 11,330 adult in-patients at 405 hospitals in 30 countries around the world [[30](#ref-jShm9uhy)]. Patients were randomized in equal proportions into four experimental and a control conditions, corresponding to four candidate treatments for COVID-19 and SOC, respectively; no placebo was administered. The 2,750 patients in the remdesivir group were administered 200 mg intravenously on the first day and 100 mg on each subsequent day until day 10 and assessed for in-hospital death (primary endpoint), duration of hospitalization, and progression to mechanical ventilation. There were also 2,708 control patients who would have been eligible and able to receive remdesivir were they not assigned to the control group. A total of 604 patients among these two cohorts deceased during initial hospitalization, with 301 in the remdesivir group and 303 in the control group. The rate ratio of death between these two groups was therefore not significant (*p* = 0.50), suggesting that the administration of remdesivir did not affect survival. The two secondary analyses similarly did not find any effect of remdesivir. Additionally, the authors compared data from their study with data from three other studies of remdesivir (including [[41](#ref-DtpdBrgt)]) stratified by supplemental oxygen status. The adjusted rate ratio for death based on this meta-analysis was 0.91. These results thus do not support the previous findings that remdesivir reduced median recovery time and mortality risk in COVID-19 patients.

In response to the results of the Solidarity trial, Gilead, which manufactures remdesivir, released a statement pointing to the fact that the Solidarity trial was not placebo-controlled or double-blind and at the time of the statement had not been peer reviewed [[57](#ref-zQT9JLP1)]; these sentiments have been echoed elsewhere [[58](#ref-vJVD0Wle)]. Other critiques of this study have noted that antivirals are not typically targeted at patients with severe illness, and therefore remdesivir could be more beneficial for patients with mild rather than severe cases [[32](#ref-xM0IhxIr),[59](#ref-pQkqi9ni)]. However, the publication associated with the trial sponsored by Gilead did purport an effect of remdesivir on patients with severe disease, identifying an 11 versus 18 day recovery period (rate ratio for recovery: 1.31, 95% CI 1.12 to 1.52), although the results of a significance test were not provided [[41](#ref-DtpdBrgt)]. Additionally, a smaller analysis of 598 patients, of whom two-thirds were randomized to receive remdesivir for either 5 or 10 days, reported a small effect of treatment with remdesivir for five days relative to standard of care in patients with moderate COVID-19 [[60](#ref-6NLZTSS0)]. These results suggest that remdesivir could improve outcomes for patients with moderate COVID-19, but that additional information would be needed to understand the effects of different durations of treatment. Therefore, the arguments put forward in defense of remdesivir do not necessarily seem robust in light of the large sample size used in the Solidarity trial, especially since the broad international nature of the Solidarity clinical trial, which included countries with a wide range of economic profiles and a variety of healthcare systems, provides a much-needed global perspective in a pandemic [[32](#ref-xM0IhxIr)]. On the other hand, only 62% of patients in the Solidarity trial were randomized on the day of admission or one day afterwards [[30](#ref-jShm9uhy)], and concerns have been raised that differences in disease progression could influence the effectiveness of remdesivir [[32](#ref-xM0IhxIr)]. Despite the findings of the Solidarity trial, remdesivir remains available for the treatment of COVID-19 in many places. Follow-up studies are needed and, in many cases, are underway to further investigate remdesivir-related outcomes, with possibilities including combinations of remdesivir with other drugs such as baricitinib, which is an inhibitor of Janus kinase 1 and 2 [[61](#ref-pDl6Q4UP)].

Similarly, the extent to which the remdesivir dosing regimen could influence outcomes continues to be under consideration. A randomized, open-label trial compared the effect of remdesivir on 397 patients with severe COVID-19 over 5 versus 10 days [[39](#ref-yTCAmOyt),[51](#ref-w5y1LWUR)], complementing the study that found that a 5-day course of remdesivir improved outcomes for patients with moderate COVID-19 but a 10-day course did not [[60](#ref-6NLZTSS0)]. Patients in the two groups were administered 200 mg of remdesivir intravenously on the first day, followed by 100 mg on the subsequent four or nine days, respectively. The two groups differed significantly in their clinical status, with patients assigned to the 10-day group having more severe illness. This study also differed from most because it included not only adults, but also pediatric patients as young as 12 years old. It reported no significant differences across several outcomes for patients receiving a 5-day or 10-day course, when correcting for baseline clinical status. The data did suggest that the 10-day course might reduce mortality in the most severe patients at day 14, but the representation of this group in the study population was too low to justify any conclusions [[51](#ref-w5y1LWUR)]. Thus, additional research is also required to determine whether the dosage and duration of remdesivir administration influences outcomes.

In summary, remdesivir is a first in class drug due to its FDA approval. Early investigations of this drug established proof of principle that drugs targeting the virus can benefit COVID-19 patients. It also shows proof of principle that SARS-CoV-2 can be targeted at the level of viral replication, since remdesivir targets the viral RNA polymerase at high potency. Moreover, one of the most successful strategies for developing therapeutics for viral diseases is to target the viral replication machinery, which are typically virally encoded polymerases. Small molecule drugs targeting viral polymerases are the backbones of treatments for other viral diseases including human immunodeficiency virus (HIV) and herpes. Notably, the HIV and herpes polymerases are a reverse transcriptase and a DNA polymerase, respectively, whereas SARS-CoV-2 encodes an RdRP, so most of the commonly used polymerase inhibitors are not likely to be active against SARS-CoV-2. In clinical use, polymerase inhibitors show short term benefits for HIV patients, but for long term benefits they must be part of combination regimens. They are typically combined with protease inhibitors, integrase inhibitors, and even other polymerase inhibitors. Additional clinical trials of remdesivir in different patient pools and in combination with other therapies will refine its use in the clinic.

#### Protease Inhibitors

Several studies showed that viral proteases play an important role in the life cycle of viruses, including coronaviruses, by modulating the cleavage of viral polyprotein precursors [[62](#ref-26dpptLw)]. Several FDA-approved drugs target proteases, including lopinavir and ritonavir for HIV infection and simeprevir for hepatitis C virus infection. In particular, serine protease inhibitors were suggested for the treatment of SARS and MERS viruses [[63](#ref-f7csoyEu)]. Recently, a study [[64](#ref-15l3di3Wj)] suggested that camostat mesylate, an FDA-approved protease inhibitor (PI) could block the entry of SARS-CoV-2 into lung cells *in vitro*. Thus far, investigation of possible PIs that could work against SARS-CoV-2 has been driven by computational predictions.

Computer-aided design allowed for the development of a Michael acceptor inhibitor, now known as N3, to target a protease critical to SARS-CoV-2 replication. Discovery of the N3 mechanism arose from interest in the two polyproteins encoded by the SARS-CoV-2 replicase gene, pp1a and pp1ab, that are critical for viral replication and transcription [[65](#ref-4Sja6dIz)]. These polyproteins must undergo proteolytic processing. This processing is usually conducted by Mpro, a 33.8-kDa SARS-CoV-2 protease that is therefore fundamental to viral replication and transcription. N3 was designed computationally [[66](#ref-15JYG0AIU)] to bind in the substrate binding pocket of the Mpro protease of SARS-like coronaviruses [[67](#ref-XfOTPQPJ)], therefore inhibiting proteolytic processing. Subsequently, the structure of N3-bound SARS-CoV-2 Mpro was solved [[65](#ref-4Sja6dIz)], confirming the computational prediction. N3 was tested *in vitro* on SARS-CoV-2-infected Vero cells, which belong to a line of cells established from the kidney epithelial cells of an African green monkey, and was found to inhibit SARS-CoV-2 [[65](#ref-4Sja6dIz)].

Although N3 is a strong inhibitor of SARS-CoV-2 *in vitro*, its safety and efficacy still need to be tested in healthy volunteers and patients. After the design and confirmation of N3 as a highly potent Michael acceptor inhibitor and the identification of Mpro’s structure [[65](#ref-4Sja6dIz),[68](#ref-10NcfBSiT)], 10,000 compounds were screened for their *in vitro* anti-Mpro activity. The six leads that were identified were ebselen, disulfiram, tideglusib, carmofur, and PX-12. *In vitro* analysis revealed that ebselen had the strongest potency in reducing the viral load in SARS-CoV-2-infected Vero cells [[65](#ref-4Sja6dIz)]. Ebselen is an organoselenium compound with anti-inflammatory and antioxidant properties [[69](#ref-17EErh01r)]. It has been proposed as a possible treatment for conditions ranging from bipolar disorder to diabetes to heart disease [[69](#ref-17EErh01r)], and a preliminary investigation of ebselen as a treatment for noise-induced hearing loss provided promising reports of its safety [[70](#ref-17QBZngoP)]. For COVID-19, the NSP5 in SARS-CoV-2 contains a cysteine at the active site of Mpro, and ebselen is able to inactivate the protease by bonding covalently with this cysteine to form a selenosulfide [[69](#ref-17EErh01r),[71](#ref-FBE30Uqz)]. Interestingly there has been some argument that selenium deficiency may be associated with more severe COVID-19 outcomes [[72](#ref-1355hoYr1),[73](#ref-bvMB3ySR),[74](#ref-11F21sY2C)], possibly indicating that its antioxidative properties are protective [[71](#ref-FBE30Uqz)]. On the other hand, ebselen and the other compounds identified are likely to be promiscuous binders, which could diminish their therapeutic potential [[65](#ref-4Sja6dIz)]. While there is clear computational and *in vitro* support for ebselen’s potential as a COVID-19 therapeutic, results from clinical trials are not yet available for this compound. However, as of July 2020, phase II clinical trials commenced to assess the effects of SPI-1005, an investigational drug from Sound Pharmaceuticals that contains ebselen [[75](#ref-G5cKNGMC)], on 60 adults presenting with each of moderate [[76](#ref-cUTgHTRj)] and severe [[77](#ref-K13XqU1J)] COVID-19.

In summary, N3 is a computationally designed molecule that inhibits the viral transcription through inhibiting Mpro. Ebselen is both a strong Mpro inhibitor and strong inhibitor of viral replication *in vitro* that was found to reduce SARS-CoV-2 viral load even more effectively than N3. Ebselen is a promising compound since its safety has been demonstrated in other indications. However, ebselen may be a false positive, since it is a promiscuous compound that can have many targets [[78](#ref-vXFGEybh)]. Therefore, the results of ongoing clinical trials are expected to help establish whether compounds with higher specificity are required.

### Broad-Spectrum Pharmaceuticals

When a virus enters a host, the host becomes the virus’s environment. Therefore, the state of the host can also influence the virus’s ability to replicate and spread. Traditionally, viral targets have been favored for pharmaceutical interventions because altering host processes is likely to be less specific than targeting the virus directly [[79](#ref-FT3Nw9xJ)]. On the other hand, targeting the host offers potential for a complementary strategy to antivirals that could broadly limit the ability of viruses to replicate [[79](#ref-FT3Nw9xJ)]. As a result, therapeutic approaches that target host proteins have become an area of interest for SARS-CoV-2. Viral entry receptors in particular have been identified as a potential target. Entry of SARS-CoV-2 into the cell depends on binding to angiotensin-converting enzyme 2 (ACE2), which is catalyzed by the enzyme encoded by *TMPRSS2* [[64](#ref-15l3di3Wj)]. In principle, drugs that reduce the expression of these proteins or sterically hinder viral interactions with them might reduce viral entry into cells.

Due to the urgent nature of the COVID-19 pandemic, many of the pharmaceutical agents that have been widely publicized as having possible therapeutic or prophylactic effects are broad-spectrum pharmaceuticals that pre-date the COVID-19 pandemic. These treatments are not specifically targeted at the virus itself or at the host receptors it relies on, but rather induce broad shifts in host biology that are hypothesized to be potential inhibitors of the virus. In most cases, interest in particular candidate medications arises because they are already available for other purposes. However, the fact that the targets of these agents are non-specific means that the mechanism of action can appear to be relevant to COVID-19 without a therapeutic or prophylactic effect being observed in clinical trials. This category of drugs has also received significant attention from the media and general public, often before rigorous testing has been able to determine their effectiveness against SARS-CoV-2.

#### ACEi and ARB

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are among today’s most commonly prescribed medications [[80](#ref-CIeWPFHG),[81](#ref-pbfxOvnK)]. In the United States, for example, they are prescribed well over 100,000,000 times annually. Data from some animal models suggest that several, but not all, ACE inhibitors and several ARBs increase ACE2 expression in the cells of some organs [[82](#ref-17xTGqKp2)]. Clinical studies have not established whether plasma ACE2 expression is increased in humans treated with these medications [[83](#ref-ZhhV4ztO)]. While randomized clinical trials are ongoing, a variety of observational studies have examined the relationship between exposure to ACE inhibitors or ARBs and outcomes in patients with COVID-19. An observational study of the association of exposure to ACE inhibitors or ARB with outcomes in COVID-19 was retracted from the *New England Journal of Medicine* [[84](#ref-10q7vcaWw)]. Moreover, because observational studies are subject to confounding, randomized controlled trials are the standard means of assessing the effects of medications, and the findings of the various observational studies bearing on this topic cannot be interpreted as indicating a protective effect of the drug [[85](#ref-19quOF2kK),[86](#ref-k5xEN3Ke)]. Several clinical trials testing the effects of ACE inhibitors or ARBs on COVID-19 outcomes are ongoing [[87](#ref-H0oEjZR8),[88](#ref-kuUcA1G9),[89](#ref-3ccJAyrG),[90](#ref-NCb9Wq2z),[91](#ref-5fkIarR7),[92](#ref-c7V9rAFR)]. These studies of randomized intervention will provide important data for understanding whether exposure to ACEis or ARBs is associated with COVID-19 outcomes. Additional information about ACE2, observational studies of ACE inhibitors and ARBs in COVID-19, and clinical trials on this topic have been summarized [[93](#ref-1Hrsy8Hiq)].

#### Hydroxychloroquine and Chloroquine

CQ and hydroxychloroquine (HCQ) are lysosomotropic agents, meaning they are weak bases that can pass through the plasma membrane. Both drugs increase cellular pH by accumulating in their protonated form inside lysosomes [[94](#ref-ggYRK4FU),[95](#ref-16IRfGFKb)]. This shift in pH inhibits the breakdown of proteins and peptides by the lysosomes during the process of proteolysis [[95](#ref-16IRfGFKb)]. A number of mechanisms have been proposed through which these drugs could influence the immune response to pathogen challenge. For example, CQ/HCQ can interfere with digestion of antigens within the lysosome and inhibit CD4 T-cell stimulation while promoting the stimulation of CD8 T-cells [[95](#ref-16IRfGFKb)]. CQ/HCQ can also decrease the production of certain key cytokines involved in the immune response, including interleukin-6 (IL-6), and inhibit the stimulation of Toll-like receptors (TLR) and TLR signaling [[95](#ref-16IRfGFKb)]. The drugs also have anti-inflammatory and photoprotective effects and may also affect rates of cell death, blood clotting, glucose tolerance, and cholesterol levels [[95](#ref-16IRfGFKb)].

Interest in CQ and HCQ for treating COVID-19 was catalyzed by a mechanism observed in *in vitro* studies of both SARS-CoV-1 and SARS-CoV-2. In one study, CQ inhibited viral entry of SARS-CoV-1 into Vero E6 cells, a cell line that was derived from Vero cells in 1968, through the elevation of endosomal pH and the terminal glycosylation of ACE2 [[96](#ref-x6nInyCf)]. Increased pH within the cell, as discussed above, inhibits proteolysis, and terminal glycosylation of ACE2 is thought to interfere with virus-receptor binding. An *in vitro* study of SARS-CoV-2 infection of Vero cells found both HCQ and CQ to be effective in inhibiting viral replication, with HCQ being more potent [[97](#ref-1GBsnkeLK)]. Additionally, an early case study of three COVID-19 patients reported the presence of antiphospholipid antibodies in all three patients [[98](#ref-8OnbWuhF)]. Antiphospholipid antibodies are central to the diagnosis of the antiphospholipid syndrome, a disorder that HCQ has often been used to treat [[99](#ref-nEaG534R),[100](#ref-rL8owM5Y),[101](#ref-134vCyU3E)]. Because the 90% effective concentration (EC90) of CQ in Vero E6 cells (6.90 μM) can be achieved in and tolerated by rheumatoid arthritis (RA) patients, it was hypothesized that it might also be possible to achieve the effective concentration in COVID-19 patients [[102](#ref-WFGcbZhe)]. Additionally, HCQ has been found to be effective in treating HIV [[103](#ref-hFGjQQN8)] and chronic Hepatitis C [[104](#ref-rQNzKxRd)]. Together, these studies triggered initial enthusiasm about the therapeutic potential for HCQ and CQ against COVID-19. HCQ/CQ has been proposed both as a treatment for COVID-19 and a prophylaxis against SARS-CoV-2 exposure, and trials often investigated these drugs in combination with azithromycin (AZ) and/or zinc supplementation. However, as more evidence has emerged, it has become clear that HCQ/CQ offer no benefits against SARS-CoV-2 or COVID-19.

##### Trials Assessing Therapeutic Administration of HCQ/CQ

The initial study evaluating HCQ as a treatment for COVID-19 patients was published on March 20, 2020 by Gautret et al. [[105](#ref-ovHLMvCi)]. This non-randomized, non-blinded, non-placebo clinical trial compared HCQ to SOC in 42 hospitalized patients in southern France. It reported that patients who received HCQ showed higher rates of virological clearance by nasopharyngeal swab on days 3-6 when compared to SOC. This study also treated six patients with both HCQ + AZ and found this combination therapy to be more effective than HCQ alone. However, the design and analyses used showed weaknesses that severely limit interpretability of results, including the lack of randomization, lack of blinding, lack of placebo, lack of Intention-To-Treat analysis, lack of correction for sequential multiple comparisons, trial arms entirely confounded by hospital, false negatives in outcome measurements, lack of trial pre-registration, and small sample size. Two of these weaknesses are due to inappropriate data analysis and can therefore be corrected *post hoc* by recalculating the p-values (lack of Intention-To-Treat analysis and multiple comparisons). However, all other weaknesses are fundamental design flaws and cannot be corrected for. Thus, the conclusions cannot be generalized outside of the study. The International Society of Antimicrobial Chemotherapy, the scientific organization that publishes the journal where the article appeared, subsequently announced that the article did not meet its expected standard for publications [[106](#ref-10J3hBiMo)], although it has not been officially retracted.

Because of the preliminary data presented in this study, HCQ treatment was subsequently explored by other researchers. About one week later, a follow-up case study reported that 11 consecutive patients were treated with HCQ + AZ using the same dosing regimen [[107](#ref-18KmvBOFr)]. One patient died, two were transferred to the intensive care unit (ICU), and one developed a prolonged QT interval, leading to discontinuation of HCQ + AZ administration. As in the Gautret et al. study, the outcome assessed was virological clearance at day 6 post-treatment, as measured from nasopharyngeal swabs. Of the ten living patients on day 6, eight remained positive for SARS-CoV-2 RNA. Like in the original study, interpretability was severely limited by the lack of a comparison group and the small sample size. However, these results stand in contrast to the claims by Gautret et al. that all six patients treated with HCQ + AZ tested negative for SARS-CoV-2 RNA by day 6 post-treatment. This case study illustrated the need for further investigation using robust study design to evaluate the efficacy of HCQ and/or CQ.

On April 10, 2020, a randomized, non-placebo trial of 62 COVID-19 patients at the Renmin Hospital of Wuhan University was released [[108](#ref-wzHb7Mj5)]. This study investigated whether HCQ decreased time to fever break or time to cough relief when compared to SOC [[108](#ref-wzHb7Mj5)]. This trial found HCQ decreased both average time to fever break and average time to cough relief, defined as mild or no cough. While this study improved on some of the methodological flaws in Gautret et al. by randomizing patients, it also had several flaws in trial design and data analysis that prevent generalization of the results. These weaknesses include the lack of placebo, lack of correction for multiple primary outcomes, inappropriate choice of outcomes, lack of sufficient detail to understand analysis, drastic disparities between pre-registration and published protocol, and small sample size. The choice of outcomes may be inappropriate as both fevers and cough may break periodically without resolution of illness. Additionally, for these outcomes, the authors reported that 23 of 62 patients did not have a fever and 25 of 62 patients did not have a cough at the start of the study, but the authors failed to describe how these patients were included in a study assessing time to fever break and time to cough relief. It is important to note here that the authors claimed “neither the research performers nor the patients were aware of the treatment assignments.” This blinding seems impossible in a non-placebo trial because at the very least, providers would know whether they were administering a medication or not, and this knowledge could lead to systematic differences in the administration of care. Correction for multiple primary outcomes can be adjusted *post hoc* by recalculating p-values, but all of the other issues were design and statistical weaknesses that cannot be corrected for. Additionally, the observation of drastic disparities between pre-registration and published protocol could indicate p-hacking [[109](#ref-XdCJ4u8O)]. The design limitations mean that the conclusions cannot be generalized outside of the study.

A second randomized trial, conducted by the Shanghai Public Health Clinical Center, analyzed whether HCQ increased rates of virological clearance at day 7 in respiratory pharyngeal swabs compared to SOC [[110](#ref-o5gwQA7W)]. This trial was published in Chinese along with an abstract in English, and only the English abstract was read and interpreted for this review. The trial found comparable outcomes in virological clearance rate, time to virological clearance, and time to body temperature normalization between the treatment and control groups. The small sample size is one weakness, with only 30 patients enrolled and 15 in each arm. This problem suggests the study is underpowered to detect potentially useful differences and precludes interpretation of results. Additionally, because only the abstract could be read, other design and analysis issues could be present. Thus, though these studies added randomization to their assessment of HCQ, their conclusions should be interpreted very cautiously. These two studies assessed different outcomes and reached differing conclusions about the efficacy of HCQ for treating COVID-19; the designs of both studies, especially with respect to sample size, meant that no general conclusions can be made about the efficacy of the drug.

Several widely reported studies on HCQ also have issues with data integrity and/or provenance. A Letter to the Editor published in *BioScience Trends* on March 16, 2020 claimed that numerous clinical trials have shown that HCQ is superior to control treatment in inhibiting the exacerbation of COVID-19 pneumonia [[111](#ref-aiItPxSY)]. This letter has been cited by numerous primary literature, review articles, and media alike [[112](#ref-1BdQKtXnY),[113](#ref-z8XnLYWM)]. However, the letter referred to 15 pre-registration identifiers from the Chinese Clinical Trial Registry. When these identifiers are followed back to the registry, most trials claim they are not yet recruiting patients or are currently recruiting patients. For all of these 15 identifiers, no data uploads or links to publications could be located on the pre-registrations. At the very least, the lack of availability of the primary data means the claim that HCQ is efficacious against COVID-19 pneumonia cannot be verified. Similarly, a recent multinational registry analysis [[114](#ref-1BApBNHvd)] analyzed the efficacy of CQ and HCQ with and without a macrolide, which is a class of antibiotics that includes Azithromycin, for the treatment of COVID-19. The study observed 96,032 patients split into a control and four treatment conditions (CQ with and without a macrolide; HCQ with and without a macrolide). They concluded that treatment with CQ and HCQ was associated with increased risk of *de novo* ventricular arrhythmia during hospitalization. However, this study has since been retracted by *The Lancet* due to an inability to validate the data used [[115](#ref-11FsxWalS)]. These studies demonstrate that increased skepticism in evaluation of the HCQ/CQ and COVID-19 literature may be warranted, possibly because of the significant attention HCQ and CQ have received as possible treatments for COVID-19 and the politicization of these drugs.

Despite the fact that the study suggesting that CQ/HCQ increased risk of ventricular arrhythmia in COVID-19 patients has now been retracted, previous studies have identified risks associated with HCQ/CQ. A patient with systemic lupus erythematosus developed a prolonged QT interval that was likely exacerbated by use of HCQ in combination with renal failure [[116](#ref-dY9kXLAS)]. A prolonged QT interval is associated with ventricular arrhythmia [[117](#ref-wy3S7Cpa)]. Furthermore, a separate study [[118](#ref-OQ0b31BA)] investigated the safety associated with the use of HCQ with and without macrolides between 2000 and 2020. The study involved 900,000 cases treated with HCQ and 300,000 cases treated with HCQ + AZ. The results indicated that short-term use of HCQ was not associated with additional risk, but that HCQ + AZ was associated with an enhanced risk of cardiovascular complications (15-20% increased risk of chest pain) and a two-fold increased risk of mortality. Therefore, whether studies utilize HCQ alone or HCQ in combination with a macrolide may be an important consideration in assessing risk. As results from initial investigations of these drug combinations have emerged, concerns about the efficacy and risks of treating COVID-19 with HCQ and CQ has led to the removal of CQ/HCQ from SOC practices in several countries [[119](#ref-1CgZR55GZ),[120](#ref-1EcscrT32)]. As of May 25, 2020, WHO had suspended administration of HCQ as part of the worldwide Solidarity Trial [[121](#ref-AMQ5402v)], and later the final results of this large-scale trial that compared 947 patients administered HCQ to 906 controls revealed no effect on the primary outcome, mortality during hospitalization (rate ratio: 1.19; *p* = 0.23)

Additional research has emerged largely identifying HCQ/CQ to be ineffective against COVID-19 while simultaneously revealing a number of significant side effects. A randomized, open-label, non-placebo trial of 150 COVID-19 patients was conducted in parallel at 16 government-designated COVID-19 centers in China to assess the safety and efficacy of HCQ [[122](#ref-RXr9BKKT)]. The trial compared treatment with HCQ in conjunction with SOC to SOC alone in 150 infected patients who were assigned randomly to the two groups (75 per group). The primary endpoint of the study was the negative conversion rate of SARS-CoV-2 in 28 days, and the investigators found no difference in this parameter between the groups. The secondary endpoints were an amelioration of the symptoms of the disease such as axillary temperature ≤36.6°C, SpO2 >94% on room air, and disappearance of symptoms like shortness of breath, cough, and sore throat. The median time to symptom alleviation was similar across different conditions (19 days in HCQ + SOC versus 21 days in SOC). Additionally, 30% of the patients receiving SOC+HCQ reported adverse outcomes compared to 8.8% of patients receiving only SOC, with the most common adverse outcome in the SOC+HCQ group being diarrhea (10% versus 0% in the SOC group, *p* = 0.004). However, there are several factors that limit the interpretability of this study. Most of the enrolled patients had mild-to-moderate symptoms (98%), and the average age was 46. SOC in this study included the use of antivirals (Lopinavir-Ritonavir, Arbidol, Oseltamivir, Virazole, Entecavir, Ganciclovir, and Interferon alfa), which appeared to introduce confounding effects. Thus, to isolate the effect of HCQ, SOC would need to exclude the use of antivirals. In this trial, the samples used to test for the presence of the SARS-CoV-2 virus were collected from the upper respiratory tract, and the authors indicated that the use of upper respiratory samples may have introduced false negatives (e.g., [[123](#ref-vr7AH83b)]). Another limitation of the study that the authors acknowledge was that the HCQ treatment began, on average, at a 16-day delay from the symptom onset. The fact that this study was open-label and lacked a placebo limits interpretation, and additional analysis is required to determine whether HCQ reduces inflammatory response. Therefore, despite some potential areas of investigation identified in *post hoc* analysis, this study cannot be interpreted as providing support for HCQ as a therapeutic against COVID-19.

Additional evidence comes from a retrospective analysis [[124](#ref-MENbRfOl)] that examined data from 368 COVID-19 patients across all United States Veteran Health Administration medical centers. The study retrospectively investigated the effect of the administration of HCQ (n=97), HCQ + AZ (n=113), and no HCQ (n=158) on 368 patients. The primary outcomes assessed were death and the need for mechanical ventilation. Standard supportive care was rendered to all patients. Due to the low representation of women (N=17) in the available data, the analysis included only men, and the median age was 65 years. The rate of death in the HCQ-only treatment condition was 27.8% and in the HCQ + AZ treatment condition, it was 22.1%. In comparison to the 14.1% rate of death in the no-HCQ cohort, these data indicated a statistically significant elevation in the risk of death for the HCQ-only group compared to the no-HCQ group (adjusted HR: 2.61, *p* = 0.03), but not for the HCQ + AZ group compared to the no-HCQ group (adjusted HR: 1.14; *p* = 0.72). Further, the risk of ventilation was similar across all three groups (adjusted HR: 1.43, *p* = 0.48 (HCQ) and 0.43, *p* = 0.09 (HCQ + AZ) compared to no HCQ). The study thus showed evidence of an association between increased mortality and HCQ in this cohort of COVID-19 patients but no change in rates of mechanical ventilation among the treatment conditions. The study had a few limitations: it was not randomized, and the baseline vital signs, laboratory tests, and prescription drug use were significantly different among the three groups. All of these factors could potentially influence treatment outcome. Furthermore, the authors acknowledge that the effect of the drugs might be different in females and pediatric subjects, since these subjects were not part of the study. The reported result that HCQ + AZ is safer than HCQ contradicts the findings of the previous large-scale analysis of twenty years of records that found HCQ + AZ to be more frequently associated with cardiac arrhythmia than HCQ alone [[118](#ref-OQ0b31BA)]; whether this discrepancy is caused by the pathology of COVID-19, is influenced by age or sex, or is a statistical artifact is not presently known.

Finally, findings from the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial were released on October 8, 2020. This study used a randomized, open-label design to study the effects of HCQ compared to SOC at 176 hospitals in the United Kingdom [[125](#ref-KwFZyfFx)]. This large study enrolled 11,197 hospitalized patients whose physicians believed it would not harm them to participate. Patients were randomized into either the control group or one of the treatment arms, with twice as many patients enrolled in the control group as any treatment group. Of the patients eligible to receive HCQ, 1,561 were randomized into the HCQ arm, and 3,155 were randomized into the control arm. The demographics of the HCQ and control groups were similar in terms of average age (65 years), proportion female (approximately 38%), ethnic make-up (73% versus 76% white), and prevalence of pre-existing conditions (56% versus 57% overall). In the HCQ arm of the study, patients received 800 mg at baseline and again after 6 hours, then 400 mg at 12 hours and every subsequent 12 hours. The primary outcome analyzed was all-cause mortality, and patient vital statistics were reported by physicians upon discharge or death, or else at 28 days following HCQ administration if they remained hospitalized. The secondary outcome assessed was the combined risk of progression to invasive mechanical ventilation or death within 28 days. By the advice of an external data monitoring committee, the HCQ arm of the study was reviewed early, leading to it being closed due a lack of support for HCQ as a treatment for COVID-19. Patients who received HCQ had a longer duration of hospitalization than patients receiving usual care, were less likely to be discharged alive within 28 days, and were more likely to progress to mechanical ventilation. This large-scale study thus builds upon studies in the United States and China to suggest that HCQ is not an effective treatment, and in fact may negatively impact COVID-19 patients due to its side effects. The rates of COVID-19-related mortality reported in the RECOVERY trial did not differ between the control and HCQ arms, but patients receiving HCQ were more likely to die due to cardiac events. Therefore, though none of the studies have been blinded, examining them together makes it clear that the available evidence points to significant dangers associated with the administration of HCQ to hospitalized COVID-19 patients, without providing any support for its efficacy.

##### HCQ for the Treatment of Mild Cases

One additional possible therapeutic application of HCQ considered was the treatment of mild COVID-19 cases in otherwise healthy individuals. This possibility was assessed in a randomized, open-label, multi-center analysis conducted in Catalonia (Spain) [[126](#ref-V8fkkVZg)]. This analysis enrolled adults 18 and older who had been experiencing mild symptoms of COVID-19 for fewer than five days. Participants were randomized into an HCQ arm (N=136) and a control arm (N=157), and those in the treatment arm were administered 800 mg of HCQ on the first day of treatment followed by 400 mg on each of the subsequent six days. The primary outcome assessed was viral clearance at days 3 and 7 following the onset of treatment, and secondary outcomes were clinical progression and time to complete resolution of symptoms. They found no significant differences between the two groups. This study thus suggests that HCQ does not improve recovery from COVID-19, even in otherwise healthy adult patients with mild symptoms.

##### Prophylactic Administration of HCQ

An initial study of the possible prophylactic application of HCQ utilized a randomized, double-blind, placebo-controlled design to analyze the administration of HCQ prophylactically [[127](#ref-NiVdIN7Z)]. Asymptomatic adults in the United States and Canada who had been exposed to SARS-CoV-2 within the past four days were enrolled in an online study to evaluate whether administration of HCQ over five days influenced the probability of developing COVID-19 symptoms over a 14-day period. Of the participants, 414 received HCQ and 407 received a placebo. No significant difference in the rate of symptomatic illness was observed between the two groups (11.8% HCQ, 14.3% placebo, *p* = 0.35). The HCQ condition was associated with side effects, with 40.1% of patients reporting side effects compared to 16.8% in the control group (*p* < 0.001). However, likely due to the high enrollment of healthcare workers (66% of participants) and the well-known side effects associated with HCQ, a large number of participants were able to correctly identify whether they were receiving HCQ or a placebo (46.5% and 35.7%, respectively). Furthermore, due to a lack of availability of diagnostic testing, only 20 of the 107 cases were confirmed with a PCR-based test to be positive for SARS-CoV-2. The rest were categorized as “probable” or “possible” cases by a panel of four physicians who were blind to the treatment status. One possible confounder is that a patient presenting one or more symptoms, which included diarrhea, was defined as a “possible” case, but diarrhea is also a common side effect of HCQ. Additionally, four of the twenty PCR-confirmed cases did not develop symptoms until after the observation period had completed, suggesting that the 14-day trial period may not have been long enough or that some participants also encountered secondary exposure events. Finally, in addition to the young age of the participants in this study, which ranged from 32 to 51, there were possible impediments to generalization introduced by the selection process, as 2,237 patients who were eligible but had already developed symptoms by day 4 were enrolled in a separate study. It is therefore likely that asymptomatic cases were over-represented in this sample, which would not have been detected based on the diagnostic criteria used. Therefore, while this study does represent the first effort to conduct a randomized, double-blind, placebo-controlled investigation of HCQ’s effect on COVID-19 symptoms in a large sample, the lack of PCR tests and several other design flaws significantly impede interpretation of the results. However, in line with the results from therapeutic studies, once again no evidence was found suggesting an effect of HCQ against COVID-19.

A second study [[128](#ref-oaqFxV4W)] examined the effect of administering HCQ to healthcare workers as a pre-exposure prophylactic. The primary outcome assessed was the conversion from SARS-CoV-2 negative to SARS-CoV-2 positive status over the 8 week study period. This study was also randomized, double-blind, and placebo-controlled, and it sought to address some of the limitations of the first prophylactic study. They aimed to enroll 200 healthcare workers, preferentially those working with COVID-19 patients, at two hospitals within the University of Pennsylvania hospital system in Philadelphia, PA. Participants were randomized 1:1 to receive either 600 mg of HCQ daily or a placebo, and their SARS-CoV-2 infection status and antibody status were assessed using RT-PCR and serological testing, respectively, at baseline, 4 weeks, and 8 weeks following the beginning of the treatment period. The statistical design of the study accounted for interim analyses at 50 and 100 participants in case efficacy or futility of HCQ for prophylaxis became clear earlier than completion of enrollment. The 139 individuals enrolled comprised a study population that was fairly young (average age 33) and made of largely of people who were white, women, and without pre-existing conditions. At the second interim analysis, more individuals in the treatment group than the control group had contracted COVID-19 (4 versus 3), causing the estimate z-score to fall below the pre-established threshold for futility. As a result, the trial was terminated early, offering additional evidence against the use of HCQ for prophylaxis.

##### Summary of HCQ/CQ Research Findings

Early *in vitro* evidence indicated that HCQ could be an effective therapeutic against SARS-CoV-2 and COVID-19, leading to significant media attention and public interest in its potential as both a therapeutic and prophylactic. Initially it was hypothesized that CQ/HCQ might be effective against SARS-CoV-2 in part because CQ and HCQ have both been found to inhibit the expression of CD154 in T-cells and to reduce TLR signaling that leads to the production of pro-inflammatory cytokines [[129](#ref-j3rGUH1f)]. Clinical trials for COVID-19 have more often used HCQ rather than CQ because it offers the advantages of being cheaper and having fewer side effects than CQ. However, research has not found support for a positive effect of HCQ on COVID-19 patients. Multiple clinical studies have already been carried out to assess HCQ as a therapeutic agent for COVID-19, and many more are in progress. To date, none of these studies have used randomized, double-blind, placebo-controlled designs with a large sample size, which would be the gold standard. Despite the design limitations (which would be more likely to produce false positives than false negatives), initial optimism about HCQ has largely dissipated. The most methodologically rigorous analysis of HCQ as a prophylactic [[127](#ref-NiVdIN7Z)] found no significant differences between the treatment and control groups, and the WHO’s global Solidarity trial similarly reported no effect of HCQ on mortality [[30](#ref-jShm9uhy)]. Thus, HCQ/CQ are not likely to be effective therapeutic or prophylactic agents against COVID-19. Additionally, one study identified an increased risk of mortality in older men receiving HCQ, and administration of HCQ and HCQ + AZ did not decrease the use of mechanical ventilation in these patients [[124](#ref-MENbRfOl)]. HCQ use for COVID-19 could also lead to shortages for anti-malarial or anti-rheumatic use, where it has documented efficacy. Despite significant early attention, these drugs appear to be ineffective against COVID-19. Several countries have now removed CQ/HCQ from their SOC for COVID-19 due to the lack of evidence of efficacy and the frequency of adverse effects.

#### Dexamethasone

Dexamethasone (9α-fluoro-16α-methylprednisolone) is a synthetic corticosteroid that binds to glucocorticoid receptors [[130](#ref-q0TqfpEr),[131](#ref-2M8wLShq)]. It was first synthesized in the late 1950s as an anti-inflammatory and has been used to treat RA and other inflammatory conditions [[132](#ref-KQ7uhAaa),[133](#ref-bSNVCQbh)]. Steroids such as dexamethasone are widely available and affordable, and they are often used to treat community-acquired pneumonia [[134](#ref-19dEKfvUE)]. A clinical trial that began in 2012 recently reported that dexamethasone may improve outcomes for patients with ARDS [[135](#ref-1DUXbHUEW)]. However, a meta-analysis of a small amount of available data about dexamethasone as a treatment for SARS suggested that it may, in fact, be associated with patient harm [[136](#ref-Ji2fchyS)]; however, these findings may have been biased by the fact that all of the studies examined were observational and a large number of inconclusive studies were not included [[137](#ref-xndHds7d)].

Dexamethasone works as an anti-inflammatory agent by binding to glucocorticoid receptors with higher affinity than endogenous cortisol [[138](#ref-1ETGa7JyL)]. In order to understand how dexamethasone reduces inflammation, it is necessary to consider the stress response broadly. In response to stress, corticotropin‐releasing hormone stimulates the release of neurotransmitters known as catecholamines, such as epinephrine, and steroid hormones known as glucocorticoids, such as cortisol [[139](#ref-jMzODpwS),[140](#ref-Riev3em1)]. While catecholamines are often associated with the fight-or-flight response, the specific role that glucocorticoids play is less clear, although they are thought to be important to restoring homeostasis [[141](#ref-JZyVNRCN)]. Immune challenge is a stressor that is known to interact closely with the stress response. The immune system can therefore interact with the central nervous system; for example, macrophages can both respond to and produce catecholamines [[139](#ref-jMzODpwS)]. Additionally, the production of both catecholamines and glucocorticoids is associated with inhibition of proinflammatory cytokines such as IL-6, IL-12, and tumor necrosis factor-α (TNF‐α) and the stimulation of anti-inflammatory cytokines such as IL-10, meaning that the stress response can regulate inflammatory immune activity [[140](#ref-Riev3em1)]. Administration of dexamethasone has been found to correspond to dose-dependent inhibition of IL-12 production, but not to affect IL-10 [[142](#ref-SiXrQUgV)]; the fact that this relationship could be disrupted by administration of a glucocorticoid-receptor antagonist suggests that it is regulated by the receptor itself [[142](#ref-SiXrQUgV)]. Thus, the administration of dexamethasone for COVID-19 is likely to simulate the release of glucocorticoids endogenously during stress, resulting in binding of the synthetic steroid to the glucocorticoid receptor and the associated inhibition of the production of proinflammatory cytokines. In this model, dexamethasone reduces inflammation by stimulating the biological mechanism that reduces inflammation following a threat such as immune challenge.

Immunosuppressive drugs such as steroids are typically contraindicated in the setting of infection [[143](#ref-nbiwprc)], but because COVID-19 results in hyperinflammation that appears to contribute to mortality via lung damage, immunosuppression may be a helpful approach to treatment [[144](#ref-3HdlV9Vf)]. The decision of whether and/or when to counter hyperinflammation with immunosuppression in the setting of COVID-19 was an area of intense debate, as the risks of inhibiting antiviral immunity needed to be weighed against the beneficial anti-inflammatory effects [[145](#ref-suHq6Qnm)]. As a result, guidelines early in the pandemic typically recommended avoiding treating COVID-19 patients with corticosteroids such as dexamethasone [[136](#ref-Ji2fchyS)].

The application of dexamethasone for the treatment of COVID-19 was evaluated as part of the multi-site RECOVERY trial in the United Kingdom [[146](#ref-pzQoUwz3)]. Over 6,000 hospitalized COVID-19 patients were assigned into the SOC or treatment (dexamethasone) arms of the trial with a 2:1 ratio. At the time of randomization, some patients were ventilated (16%), others were on non-invasive oxygen (60%), and others were breathing independently (24%). Patients in the treatment arm were administered dexamethasone either orally or intravenously at 6 mg per day for up to 10 days. The primary end-point was the patient’s status at 28-days post-randomization (mortality, discharge, or continued hospitalization), and secondary outcomes analyzed included the progression to invasive mechanical ventilation over the same period. The 28-day mortality rate was found to be lower in the treatment group than in the SOC group (21.6% vs 24.6%, *p* < 0.001). However, this finding was driven by differences in mortality among patients who were receiving mechanical ventilation or supplementary oxygen at the start of the study. The report indicated that dexamethasone reduced 28-day mortality relative to SOC in patients who were ventilated (29.3% versus 41.4%) and among those who were receiving oxygen supplementation (23.3% versus 26.2%) at randomization, but not in patients who were breathing independently (17.8% versus 14.0%). One possible confounder is that patients receiving mechanical ventilation tended to be younger than patients who were not receiving respiratory support (by 10 years on average) and to have had symptoms for a longer period. However, adjusting for age did not change the conclusions, although the duration of symptoms was found to be significantly associated with the effect of dexamethasone administration. These findings also suggested that dexamethasone may have reduced progression to mechanical ventilation, especially among patients who were receiving oxygen support at randomization. Thus, this large, randomized, and multi-site, albeit not placebo-controlled, study suggests that administration of dexamethasone to patients who are unable to breathe independently may significantly improve survival outcomes. Additionally, dexamethasone is a widely available and affordable medication, raising the hope that it could be made available to COVID-19 patients globally.

The results of the RECOVERY trial’s analysis of dexamethasone suggest that this therapeutic is effective primarily in patients who had been experiencing symptoms for at least seven days and patients who were not breathing independently [[147](#ref-H3C2PalE)]. A meta-analysis that evaluated the results of the RECOVERY trial alongside trials of other corticosteroids, such as hydrocortisone, similarly concluded that corticosteroids may be beneficial to patients with severe COVID-19 who are receiving oxygen supplementation [[148](#ref-wNXTNffA)]. Thus, it seems likely that dexamethasone is useful for treating inflammation associated with immunopathy or cytokine release syndrome (CRS). In fact, corticosteroids such as dexamethasone are sometimes used to treat CRS [[149](#ref-H70g2GF9)]. It is not surprising that administration of an immunosuppressant would be most beneficial when the immune system was dysregulated towards inflammation. However, it is also unsurprising that care must be taken in administering an immunosuppressant to patients fighting a viral infection. In particular, the concern has been raised that treatment with dexamethasone might increase patient susceptibility to concurrent (e.g., nosocomial) infections [[150](#ref-EgvIETTq)]. Additionally, the drug could potentially slow viral clearance and inhibit patients’ ability to develop antibodies to SARS-CoV-2 [[136](#ref-Ji2fchyS),[150](#ref-EgvIETTq)], and the lack of data about viral clearance has been put forward as a major limitation of the RECOVERY trial [[151](#ref-TytQ90Bl)]. Furthermore, dexamethasone has been associated with side effects that include psychosis, glucocorticoid-induced diabetes, and avascular necrosis [[136](#ref-Ji2fchyS)], and the RECOVERY trial did not report outcomes with enough detail to be able to determine whether they observed similar complications. The effects of dexamethasone have also been found to differ among populations, especially in high-income versus middle- or low-income countries [[152](#ref-1E4Qx2UqB)]. However, since the RECOVERY trial’s results were released, strategies have been proposed for administering dexamethasone alongside more targeted treatments to minimize the likelihood of negative side effects [[150](#ref-EgvIETTq)]. Given the available evidence, dexamethasone is currently the most promising treatment for severe COVID-19.

## Biologics

Biologics are produced from components of living organisms or viruses. They include treatments such as humanized monoclonal antibodies (mAb), tocilizumab (TCZ), and neutralizing antibodies (nAbs), and can also include prophylactics such as vaccines. Historically produced from animal tissue, biologics have become increasingly feasible to produce as recombinant DNA technologies have advanced [[153](#ref-1ALDN7rfe)]. Often, they are glycoproteins or peptides [[154](#ref-OgYDNJt3)], but whole viruses can also be used therapeutically or prophylactically, not only for vaccines but also as vectors for gene therapy or therapeutic proteins or for oncolytic virotherapy [[155](#ref-GO8FwtPx)]. They are typically catabolized by the body to their amino acid components [[154](#ref-OgYDNJt3)]. There are many differences on the development side between biologics and synthesized pharmaceuticals, such as small molecule drugs. Biologics are typically orders of magnitude larger than small molecule drugs, and their physiochemical properties are often much less understood [[154](#ref-OgYDNJt3)]. They are often heat sensitive, and their toxicity can vary, as it is not directly associated with the primary effects of the drug [[154](#ref-OgYDNJt3)]. However, this class includes some extremely significant medical breakthroughs, including insulin for the management of diabetes and the smallpox vaccine. As a result, biologics are another possible avenue through which the pharmacological management of SARS-CoV-2 infection can be approached.

### Tocilizumab

TCZ is a receptor antibody that was developed to manage chronic inflammation caused by the continuous synthesis of the cytokine IL-6 [[156](#ref-NDRyNd61)]. IL-6 is a pro-inflammatory cytokine belonging to the interleukin family, which is comprised by immune system regulators that are primarily responsible for immune cell differentiation. Often used to treat conditions such as RA [[156](#ref-NDRyNd61)], TCZ has become a pharmaceutical of interest for the treatment of COVID-19 because of the role IL-6 plays in this disease. While secretion of IL-6 can be associated with chronic conditions, it is a key player in the innate immune response and is secreted by macrophages in response to the detection of pathogen-associated molecular patterns and damage-associated molecular patterns [[156](#ref-NDRyNd61)]. An analysis of 191 in-patients at two Wuhan hospitals revealed that blood concentrations of IL-6 differed between patients who did and did not recover from COVID-19. Patients who ultimately deceased had higher IL-6 levels at admission than those who recovered [[157](#ref-10THxyeCg)]. Additionally, IL-6 levels remained higher throughout the course of hospitalization in the patients who ultimately deceased [[157](#ref-10THxyeCg)]. This finding provided some early evidence that COVID-19 deaths may be induced by the hyperactive immune response, often referred to as CRS or cytokine storm syndrome (CSS), as IL-6 plays a key role in this response [[158](#ref-bZMKqj6e)]. In this context, the observation of elevated IL-6 in patients who died may reflect an over-production of proinflammatory interleukins, suggesting that TCZ could potentially palliate some of the most severe symptoms of COVID-19 associated with increased cytokine production.

Human IL-6 is a 26-kDa glycoprotein that consists of 184 amino acids and contains two potential N-glycosylation sites and four cysteine residues. It binds to a type I cytokine receptor (IL-6Rα or glycoprotein 80) that exists in both membrane-bound (IL-6Rα) and soluble (sIL-6Rα) forms [[159](#ref-VXDsRwHC)]. It is not the binding of IL-6 to the receptor that initiates pro- and/or anti-inflammatory signaling, but rather the binding of the complex to another subunit, known as IL-6Rβ or glycoprotein 130 (gp13) [[159](#ref-VXDsRwHC),[160](#ref-14xZS2Gic)]. Unlike membrane-bound IL-6Rα, which is only found on hepatocytes and some types of leukocytes, gp130 is found on most cells [[161](#ref-LIqxTdN)]. When IL-6 binds to sIL-6Rα, the complex can then bind to a gp130 protein on any cell [[161](#ref-LIqxTdN)]. The binding of IL-6 to IL-6Rα is termed classical signaling, while its binding to sIL-6Rα is termed trans-signaling [[161](#ref-LIqxTdN),[162](#ref-1BxkPZYnj),[163](#ref-1EEloBjzn)]. These two signaling processes are thought to play different roles in health and illness. For example, trans-signaling may play a role in the proliferation of mucosal T-helper TH2 cells associated with asthma, while an earlier step in this proliferation process may be regulated by classical signaling [[161](#ref-LIqxTdN)]. Similarly, IL-6 is known to play a role in Crohn’s Disease via trans-, but not classical, signaling [[161](#ref-LIqxTdN)]. Both classical and trans-signaling can occur through three independent pathways: the Janus-activated kinase-STAT3 pathway, the Ras/Mitogen-Activated Protein Kinases (MAPK) pathway and the Phosphoinositol-3 Kinase/Akt pathway [[159](#ref-VXDsRwHC)]. These signaling pathways are involved in a variety of different functions, including cell type differentiation, immunoglobulin synthesis, and cellular survival signaling pathways, respectively [[159](#ref-VXDsRwHC)]. The ultimate result of the IL-6 cascade is to direct transcriptional activity of various promoters of pro-inflammatory cytokines, such as IL-1, TFN, and even IL-6 itself, through the activity of NF-κB [[159](#ref-VXDsRwHC)]. IL-6 synthesis is tightly regulated both transcriptionally and post-transcriptionally, and it has been shown that viral proteins can enhance transcription of the IL-6 gene by strengthening the DNA-binding activity between several transcription factors and IL-6 gene-cis-regulatory elements [[164](#ref-1H8o8TFtM)]. Therefore, drugs inhibiting the binding of IL-6 to IL-6Rα or sIL-6Rα are of interest for combating the hyperactive inflammatory response characteristic of CRS and CSS. TCZ is a humanized monoclonal antibody that binds both to the insoluble and soluble receptor of IL-6, providing de facto inhibition of the IL-6 immune cascade.

Tocilizumab is being administered either as an intervention or as concomitant medication in 77 interventional COVID-19 clinical trials (Figure [2](#fig:ebm-trials)). No randomized, placebo-controlled studies of TCZ have currently released results. Therefore, no conclusions can be drawn about its efficacy for the treatment of COVID-19. However, early interest in TCZ as a possible treatment for COVID-19 emerged from a very small retrospective study in China that examined 20 patients with severe symptoms in early February 2020 and reported rapid improvement in symptoms following treatment with TCZ [[165](#ref-bj2feMy4)]. Subsequently, a number of retrospective studies have been conducted in several countries. Many studies use a retrospective, observational design, where they compare outcomes for COVID-19 patients who received TCZ to those who did not over a set period of time. For example, one of the largest retrospective, observational analysis released to date [[166](#ref-ayc7zYqi)] compared the rates at which patients who received TCZ deceased or progressed to invasive medical ventilation over a 14-day period compared to patients receiving only SOC. Under this definition, SOC could include other drugs such as HCQ, azithromycin, lopinavir-ritonavir or darunavir-cobicistat, or heparin. While this study was not randomized, a subset of patients who were eligible to receive TCZ were unable to obtain it due to shortages; however, these groups were not directly compared in the analysis. After adjusting for variables such as age, sex, and SOFA (sequential organ failure assessment) score, they found that patients treated with TCZ were less likely to progress to invasive medical ventilation and/or death (adjusted HR = 0.61, CI 0.40-0.92, *p* = 0.020), although analysis of death and ventilation separately suggests that this effect may have been driven by differences in the death rate (20% of control versus 7% of TCZ-treated patients). They reported particular benefits for patients whose PaO2/FiO2 ratio, also known as the Horowitz Index for Lung Function, fell below a 150 mm Hg threshold. They found no differences between groups administered subcutaneous versus intravenous TCZ.

Another retrospective observational analysis of interest examined the charts of patients at a hospital in Connecticut, USA where 64% of all 239 COVID-19 patients in the study period were administered TCZ based on assignment by a standardized algorithm [[167](#ref-Wt9vgKLY)]. They found that TCZ administration was associated with more similar rates of survivorship in patients with severe versus nonsevere COVID-19 at intake, defined based on the amount of supplemental oxygen needed. They therefore proposed that their algorithm was able to identify patients presenting with or likely to develop CRS as good candidates for TCZ. This study also reported higher survivorship in Black and Hispanic patients compared to white patients when adjusted for age. The major limitation with interpretation for these studies is that there may be clinical characteristics that influenced medical practitioners decisions to administer TCZ to some patients and not others. One interesting example therefore comes from an analysis of patients at a single hospital in Brescia, Italy, where TCZ was not available for a period of time [[168](#ref-luPHOS0m)]. This study compared COVID-19 patients admitted to the hospital before and after March 13, 2020, when the hospital received TCZ. Therefore, patients who would have been eligible for TCZ prior to this arbitrary date did not receive it as treatment, making this retrospective analysis something of a natural experiment. Despite this design, demographic factors did not appear to be consistent between the two groups, and the average age of the control group was older than the TCZ group. The control group also had a higher percentage of males and a higher incidence of comorbidities such as diabetes and heart disease. All the same, the multivariate HR, which adjusted for these clinical and demographic factors, found a significant difference between survival in the two groups (HR=0.035, CI=0.004-0.347, *p* = 0.004). They reported improvement of survival outcomes after the addition of TCZ to their SOC regime, with 11 of 23 patients (47.8%) admitted prior to March 13th dying compared to 2 of 62 (3.2%) admitted afterwards. They also reported a reduced progression to mechanical ventilation in the TCZ group. However, this study also holds a significant limitation: the time delay between the two groups means that knowledge about how to treat the disease likely improved over this timeframe as well. All the same, the results of these observational retrospective studies provide support for TCZ as a pharmaceutical of interest for follow-up in clinical trials.

In addition to the retrospective observational studies, other analysis have utilized a retrospective case-control design to match pairs of patients with similar baseline characteristics, only one of whom received TCZ for COVID-19. In one such study, TCZ was significantly associated with a reduced risk of progression to ICU admission or death [[169](#ref-17hgtBpcV)]. This study examined only 20 patients treated with TCZ (all but one of the patients treated with TCZ in the hospital during the study period) and compared them to 25 patients receiving SOC. For the combined primary endpoint of death and/or ICU admission, only 25% of patients receiving TCZ progressed to an endpoint compared to 72% in the SOC group (*p* = 0.002, presumably based on a chi-square test based on the information provided in the text). When the two endpoints were examined separately, progression to invasive medical ventilation remained significant (32% SOC compared to 0% TCZ, *p* = 0.006) but not for mortality (48% SOC compared to 25% TCZ, *p* = 0.066). In contrast, a study that compared 96 patients treated with TCZ to 97 patients treated with SOC only in New York City found that differences in mortality did not differ between the two groups, but that this difference did become significant when intubated patients were excluded from the analysis [[170](#ref-WEqfULN1)]. Taken together, these findings suggest that future clinical trials of TCZ may want to include intubation as an endpoint. However, these studies should be approached with caution, not only because of the small number of patients enrolled and the retrospective design, but also because they performed a large number of statistical tests and did not account for multiple hypothesis testing. These last findings highlight the need to search for a balance between impairing a harmful immune response, such as the one generated during CRS and CSS, and preventing the worsening of the clinical picture of the patients by potential new viral infections.

Though data about TCZ for COVID-19 is still only just emerging, some meta-analyses and systematic reviews have investigated the available data. One meta-analysis [[171](#ref-3yV2bL9S)] evaluated 19 studies published or released as preprints prior to July 1, 2020 and found that the overall trends were supportive of the frequent conclusion that TCZ does improve survivorship, with a significant HR of 0.41 (*p* < 0.001). This trend improved when they excluded studies that administered a steroid alongside TCZ, with a significant HR of 0.04 (*p* < 0.001). They also found some evidence for reduced invasive ventilation or ICU admission, but only when excluding all studies except a small number whose estimates were adjusted for the possible bias introduced by the challenges of stringency during the enrollment process. A systematic analysis of sixteen case-control studies of TCZ estimated an odds ratio of 0.453 (95% CI 0.376–0.547, *p* < 0.001), suggesting possible benefits associated with TCZ treatment [[172](#ref-WmK4YTdx)]. Although these estimates are similar, it is important to note that they are drawing from the same literature and are therefore likely to be affected by the same biases in publication. A second systematic review of studies investigating TCZ treatment for COVID-19 analyzed 31 studies that had been published or released as pre-prints and reported that none carried a low risk of bias [[173](#ref-h4reluu)]. Therefore, the present evidence is not likely to be sufficient for conclusions about the efficacy of TCZ.

Additionally, there are possible risks associated with the administration of TCZ for COVID-19. TCZ has been used for over a decade to treat RA [[174](#ref-CRriJXDk)], and a recent study found the drug to be safe for pregnant and breastfeeding women [[175](#ref-6xLhs9st)]. However, TCZ may increase the risk of developing infections [[174](#ref-CRriJXDk)], and RA patients with chronic hepatitis B infections had a high risk of hepatitis B virus reactivation when TCZ was administered in combination with other RA drugs [[176](#ref-IJzmtJOr)]. As a result, TCZ is contraindicated in patients with active infections such as tuberculosis [[177](#ref-SiOKIbl3)]. Previous studies have investigated, with varying results, a possible increased risk of infection in RA patients administered TCZ [[178](#ref-6Agll71m),[179](#ref-zRRSvckT)], although another study reported that the incidence rate of infections was higher in clinical practice RA patients treated with TCZ than in the rates reported by clinical trials [[180](#ref-TgV8gb30)]. In the investigation of 544 Italian COVID-19 patients, the group treated with TCZ was found to be more likely to develop secondary infections, with 24% compared to 4% in the control group [[166](#ref-ayc7zYqi)]. Reactivation of hepatitis B and herpes simplex virus 1 was also reported in a small number of patients in this study, all of whom were receiving TCZ. A July 2020 case report described negative outcomes of two COVID-19 patients after receiving TCZ, including one death; however, both patients were intubated and had entered septic shock prior to receiving TCZ [[181](#ref-p0tzgJvA)], likely indicating a severe level of cytokine production. Additionally, D-dimer and sIL2R levels were reported by one study to increase in patients treated with TCZ, which raised concerns because of the potential association between elevated D-dimer levels and thrombosis and between sIL2R and diseases where T-cell regulation is compromised [[167](#ref-Wt9vgKLY)]. An increased risk of bacterial infection was also identified in a systematic review of the literature, based on the unadjusted estimates reported [[171](#ref-3yV2bL9S)]. TCZ administration to COVID-19 patients is not without risks, may introduce additional risk of developing secondary infections, and should be approached especially cautiously for patients who have latent viral infections.

In summary, approximately 25% of coronavirus patients develop ARDS, which is caused by an excessive early response of the immune system which can be a component of CRS [[167](#ref-Wt9vgKLY)] and CSS [[177](#ref-SiOKIbl3)]. This overwhelming inflammation is triggered by IL-6. TCZ is an inhibitor of IL-6 and therefore may neutralize the inflammatory pathway that leads to the cytokine storm. While the mechanism suggests TCZ could be beneficial for the treatment of COVID-19 patients experiencing excessive immune activity, no randomized controlled trials are available assessing its effect. However, small initial studies have found preliminary indications that TCZ may reduce progression to invasive medical ventilation and/or death. It should be noted that SOC varied widely across retrospective studies, with one study administering HCQ, lopinavir-ritonavir, antibiotics, and/or heparin as part of SOC. Interest in TCZ as a treatment for COVID-19 was supported by two meta-analyses [[171](#ref-3yV2bL9S),[182](#ref-ZHqWXFcN)], but a third meta-analysis found that all of the available literature carries a risk of bias, with even the largest available TCZ studies to date carrying a moderate risk of bias under the ROBINS-I criteria [[173](#ref-h4reluu)]. Additionally, different studies used different dosages, number of doses, and methods of administration. Ongoing research may be needed to optimize administration of TCZ [[183](#ref-hvOwSJvK)], although similar results were reported by one study for intravenous and subcutaneous administration [[166](#ref-ayc7zYqi)]. Clinical trials that are in progress are likely to provide additional insight into the effectiveness of this drug for the treatment of COVID-19 along with how it should be administered.

### Neutralizing Antibodies

Monoclonal antibodies have revolutionized the way we treat human diseases. They have become some of the best-selling drugs in the pharmaceutical market in recent years [[184](#ref-1AKi0FYUB)]. There are currently 79 FDA approved mAbs on the market, including antibodies for viral infections (e.g. Ibalizumab for HIV and Palivizumab for RSV) [[184](#ref-1AKi0FYUB),[185](#ref-yumBaJ6U)]. Virus-specific nAbs commonly target viral surface glycoproteins or host structures, thereby inhibiting viral entry through receptor binding interference [[186](#ref-dUnB3gD6),[187](#ref-cwbHiM1o)]. This section discusses current efforts in developing nAbs against SARS-CoV-2 and how expertise gained from previous approaches for MERS-CoV and SARS-CoV-1 may benefit antibody development.

#### Spike (S) Neutralizing Antibody

During the first SARS epidemic in 2002, nAbs were found in SARS-CoV-1-infected patients [[188](#ref-3gp7t98X),[189](#ref-KULxo48U)]. Several studies following up on these findings identified various S-glycoprotein epitopes as the major targets of nAbs against SARS-CoV-1 [[190](#ref-MTcTiS7i)]. The passive transfer of immune serum containing nAbs from SARS-CoV-1-infected mice resulted in protection of naïve mice from viral lower respiratory tract infection upon intranasal challenge [[191](#ref-rXzkS3gA)]. Similarly, a meta-analysis suggested that administration of plasma from recovered SARS-CoV-1 patients reduced mortality upon SARS-CoV-1 infection [[192](#ref-RRx6YovP)]. Similar results were observed in MERS-CoV infection during the second coronavirus-related epidemic of the 21st century. In these cases, nAbs were identified against various epitopes of the receptor binding domain (RBD) of the S glycoprotein [[193](#ref-Ou3P9pGV),[194](#ref-b4TFEgIi)]. Coronaviruses use trimeric spike (S) glycoproteins on their surface to bind to the host cell, allowing for cell entry [[64](#ref-15l3di3Wj),[195](#ref-qcVbT0w4)]. Each S glycoprotein protomer is comprised of an S1 domain, also called the RBD, and an S2 domain. The S1 domain binds to the host cell while the S2 domain facilitates the fusion between the viral envelope and host cell membranes [[190](#ref-MTcTiS7i)]. Although targeting of the host cell enzyme ACE2 shows efficacy in inhibiting SARS-CoV-2 infection [[196](#ref-2QTH37Xi)], given the physiological relevance of ACE2 [[197](#ref-1GLr0EJU)], it would be favorable to target virus-specific structures rather than host receptors. This concern underlies the rationale for developing nAbs against the S glycoprotein, disrupting its interaction with ACE2 and other potential entry points and thereby inhibiting viral entry.

The first human nAb against SARS-CoV-2 targeting the S glycoproteins was developed using hybridoma technology [[198](#ref-XcuzhxrJ)], where antibody-producing B-cells developed by mice can be inserted into myeloma cells to produce a hybrid cell line (the hybridoma) that is grown in culture. The 47D11 clone was able to cross-neutralize SARS-CoV-1 and SARS-CoV-2 by a mechanism that is different from receptor binding interference. The exact mechanism of how this clone neutralizes SARS-CoV-2 and inhibits infection *in vitro* remains unknown, but a potential mechanism might be antibody-induced destabilization of the membrane prefusion structure [[198](#ref-XcuzhxrJ),[199](#ref-Ftbm1M9p)]. The ability of this antibody to prevent infection at a feasible dose needs to be validated *in vivo*, especially since *in vitro* neutralization effects have been shown to not be reflective of *in vivo* efficacy [[200](#ref-O1whWg6Q)]. Only a week later, a different group successfully isolated multiple nAbs targeting the RBD of the S glycoprotein from blood samples taken from COVID-19 patients in China [[201](#ref-GhJYjnft)]. Interestingly, the patient-isolated antibodies did not cross-react with RBDs from SARS-CoV-1 and MERS-CoV, although cross-reactivity to the trimeric spike proteins of SARS-CoV-1 and MERS-CoV was observed. This finding suggests that the RBDs between the three coronavirus species are immunologically distinct and that the isolated nAbs targeting the RBD of SARS-CoV-2 are species specific. While this specificity is desirable, it also raises the question of whether these antibodies are more susceptible to viral escape mechanisms. Viral escape is a common resistance mechanism to nAb therapy due to selective pressure from nAbs [[202](#ref-pUnzB8wV),[203](#ref-14motyCOm)]. For HIV, broadly neutralizing antibodies (bnAbs) targeting the CD4 binding site (CD4bs) show greater neutralization breadth than monoclonal antibodies, which target only specific HIV strains [[204](#ref-oGHFF5Cm)]. For MERS-CoV, a combination of multiple nAbs targeting different antigenic sites prevented neutralization escape [[205](#ref-hvjXMm9H)]. It was found that the different antibody isolates did not target the same epitopes, suggesting that using them in combination might produce a synergistic effect that prevents viral escape [[201](#ref-GhJYjnft)]. It was also demonstrated that binding affinity of the antibodies does not reflect their capability to compete with ACE2 binding. Furthermore, no conclusions about correlations between the severity of disease and the ability to produce nAbs can be drawn at this point. Rather, higher nAb titers were more frequently found in patients with severe disease. Correspondingly, higher levels of anti-spike IgG were observed in patients that deceased from infection compared to patient that recovered [[206](#ref-tC5vJmwj)].

Results from the SARS and MERS epidemics thus provide valuable lessons for the design of nAbs for the current outbreak. The findings for SARS-CoV-1 and MERS-CoV can aid in identifying which structures constitute suitable targets for nAbs, despite the fact that the RBD appears to be distinct between the three coronavirus species. These studies also suggest that a combination of nAbs targeting distinct antigens might be necessary to provide protection [[205](#ref-hvjXMm9H)]. The biggest challenge remains identifying antibodies that not only bind to their target, but also prove to be beneficial for disease management. On that note, a recently published study indicates that anti-spike antibodies could make the disease worse rather than eliminating the virus [[206](#ref-tC5vJmwj)]. These findings underscores our current lack of understanding the full immune response to SARS-CoV-2.

### Interferons

IFNs are a family of cytokines critical to activating the innate immune response against viral infections. Interferons are classified into three categories based on their receptor specificity: types I, II and III [[158](#ref-bZMKqj6e)]. Specifically, IFNs I (IFN-𝛼 and 𝛽) and II (IFN-𝛾) induce the expression of antiviral proteins [[207](#ref-LtFtUo2P)]. Among these IFNs, IFN-𝛽 has already been found to strongly inhibit the replication of other coronaviruses, such as SARS-CoV-1, in cell culture, while IFN-𝛼 and 𝛾 were shown to be less effective in this context [[207](#ref-LtFtUo2P)]. There is evidence that patients with higher susceptibility to ARDS indeed show deficiency in IFN-𝛽. For instance, infection with other coronaviruses impairs IFN-𝛽 expression and synthesis, allowing the virus to escape the innate immune response [[208](#ref-Nfu9kiae)]. On March 18 2020, Synairgen plc received approval to start a phase II trial for SNG001, an IFN-𝛽-1a formulation to be delivered to the lungs via inhalation [[209](#ref-5GxCGzrT)]. SNG001, which contains recombinant interferon beta-1a, was previously shown to be effective in reducing viral load in an *in vivo* model of swine flu and *in vitro* models of other coronavirus infections [[210](#ref-7k9Wp9or)]. In July, a press release from Synairgen stated that SNG001 reduced progression to ventilation in a double-blind, placebo-controlled, multi-center study of 101 patients with an average age in the late 50s [[211](#ref-bD1bgfSb)]. These results were subsequently published in November 2020 [[212](#ref-qFDbLzcP)]. The study reports that the participants were assigned at a ratio of 1:1 to receive either SNG001 or a placebo that lacked the active compound, by inhalation for up to 14 days. The primary outcome they assessed was the change in patients’ score on the WHO Ordinal Scale for Clinical Improvement (OSCI) at trial day 15 or 16. SNG001 was associated with an odds ratio (OR) of 2.32 (95% CI 1.07 – 5.04, *p* = 0.033) in the intention-to-treat analysis and 2.80 (95% CI 1.21 – 6.52, *p* = 0.017) in the per-protocol analysis, corresponding to significant improvement in the SNG001 group on the OSCI at day 15/16. Some of the secondary endpoints analyzed also showed differences: at day 28, the OR for clinical improvement on the OSCI was 3.15 (95% CI 1.39 – 7.14, *p* = 0.006), and the odds of recovery at day 15/16 and at day 28 were also significant between the two groups. Thus, this study suggested that IFN-𝛽1 administered via SNG001 may improve clinical outcomes.

In contrast, the WHO Solidarity trial reported no significant effect of IFN-𝛽1a on patient survival during hospitalization [[30](#ref-jShm9uhy)]. Here, the primary outcome analyzed was in-hospital mortality, and the rate ratio for the two groups was 1.16 (95% CI, 0.96 to 1.39; *p* = 0.11) administering IFN-𝛽-1a to 2050 patients and comparing their response to 2,050 controls. However, there are a few reasons that the different findings of the two trials might not speak to the underlying efficacy of this treatment strategy. One important consideration is the stage of COVID-19 infection analyzed in each study. The Synairgen trial enrolled only patients who were not receiving invasive ventilation, corresponding to a less severe stage of disease than many patients enrolled in the SOLIDARITY trial, as well as a lower overall rate of mortality [[213](#ref-11hbhD5Rk)]. Additionally, the methods of administration differed between the two trials, with the SOLIDARITY trial administering IFN-𝛽-1a subcutaneously [[213](#ref-11hbhD5Rk)]. The differences in findings between the studies suggests that the method of administration might be relevant to outcomes, with nebulized IFN-𝛽-1a more directly targeting receptors in the lungs. A trial that analyzed the effect of subcutaneously administered IFN-β-1a on patients with ARDS between 2015 and 2017 had also reported no effect on 28-day mortality [[214](#ref-B2urVDo5)], while a smaller study analyzing the effect of subcutaneous IFN administration did find a significant improvement in 28-day mortality for COVID-19 [[215](#ref-xMRJgRES)]. At present, several ongoing clinical trials are investigating the potential effects of IFN-𝛽-1a, including in combination with therapeutics such as remdesivir [[216](#ref-17so9kzfj)] and administered via inhalation [[209](#ref-5GxCGzrT)]. Thus, as additional information becomes available, a more detailed understanding of whether and under which circumstances IFN-𝛽-1a is beneficial to COVID-19 patients should develop.

## Discussion

With the emergence of the COVID-19 pandemic caused by the coronavirus SARS-CoV-2, the development and identification of therapeutic and prophylactic interventions became issues of international urgency. In previous outbreaks of HCoV, namely SARS and MERS, the development of these interventions was very limited. As research has progressed, several potential approaches to treatment have emerged (Figure [3](#fig:therapeutics)). Most notably, remdesivir has been approved by the FDA for the treatment of COVID-19, and dexamethasone, which was approved by the FDA in 1958, has been found to improve outcomes for patients with severe COVID-19. Other potential therapies are being still being explored and require additional data (Figure [2](#fig:ebm-trials)). As more evidence becomes available, the potential for existing and novel therapies to improve outcomes for COVID-19 patients will become better understood.



Figure 3: **Mechanism of Action for Potential Therapeutics** Potential therapeutics currently being studied can target the SARS-CoV-2 virus or modify the host environment through many different mechanisms. Here, the relationship between the virus and several therapeutics described above are visualized.

Insights into the pathogenesis of and immune response to SARS-CoV-2 (see [[1](#ref-r366f5T3)]) have also guided the identification of potential prophylactics and therapeutics. As cases have become better characterized, it has become evident that many patients experience an initial immune response to the virus that is typically characterized by fever, cough, dyspnea, and related symptoms. However, the most serious concern is CRS, when the body’s immune response becomes dysregulated, resulting in an extreme inflammatory response. The RECOVERY trial, a large-scale, multi-arm trial enrolling about 15% of all COVID-19 patients in the United Kingdom, was the first to identify that the widely available steroid dexamethasone seems to be beneficial for patients suffering from this immune dysregulation [[146](#ref-pzQoUwz3)]. The results of efforts to identify therapeutic treatments to treat patients early in the course of infection have been more ambiguous. Early interest in the drugs HCQ and CQ yielded no promising results from studies with robust experimental designs. On the other hand, the experimental drug remdesivir, which was developed as a candidate therapeutic for EVD, has received enough support from early analyses to receive FDA approval, although results have been mixed. The potential for other drugs, such as tocilizumab, to reduce recovery time remains unclear, but some early results were promising.

One additional concern is that the presentation of COVID-19 appears to be heterogeneous across the lifespan. Many adult cases, especially in younger adults, present with mild symptoms or even asymptomatically, while others, especially in older adults, can be severe or fatal. In children, the SARS-CoV-2 virus can present as two distinct diseases, COVID-19 or MIS-C. The therapeutics and prophylactics discussed here were primarily tested in adults, and additional research is needed to identify therapeutics that address the symptoms characteristic of pediatric COVID-19 and MIS-C cases.

### Potential Avenues of Interest for Therapeutic Development

Given what is currently known about these therapeutics for COVID-19, a number of related therapies beyond those explored above may also prove to be of interest. For example, the demonstrated benefit of dexamethasone and the ongoing potential of tocilizumab for treatment of COVID-19 suggests that other anti-inflammatory agents might also hold value for the treatment of COVID-19. Current evidence supporting the treatment of severe COVID-19 with dexamethasone suggests that the need to curtail the cytokine storm inflammatory response transcends the risks of immunosuppression, and other anti-inflammatory agents may therefore benefit patients in this phase of the disease. While dexamethasone is considered widely available and generally affordable, the high costs of biologics such as tocilizumab therapy may present obstacles to wide-scale distribution of this drug if it proves of value. At the doses used for RA patients, the cost for tocilizumab ranges from $179.20 to $896 per dose for the IV form and $355 for the pre-filled syringe [[217](#ref-7fZ9eyMk)]. Several other anti-inflammatory agents used for the treatment of autoimmune diseases may also be able to counter the effects of the cytokine storm induced by the virus, and some of these, such as cyclosporine, are likely to be more cost-effective and readily available than biologics [[218](#ref-trWLoLFz)]. While tocilizumab targets IL-6, several other inflammatory markers could be potential targets, including TNF-α. Inhibition of TNF-α by a compound such as Etanercept was previously suggested for treatment of SARS-CoV-1 [[219](#ref-LDQlolY3)] and may be relevant for SARS-CoV-2 as well. Another anti-IL-6 antibody, sarilumab, is also being investigated [[220](#ref-4DAIEbQF),[221](#ref-amy3rDsj)]. Baricitinib and other small molecule inhibitors of the Janus-activated kinase pathway also curtail the inflammatory response and have been suggested as potential options for SARS-CoV-2 infections [[222](#ref-WF7ymA4m)]. Baricitinib, in particular, may be able to reduce the ability of SARS-CoV-2 to infect lung cells [[223](#ref-uCns3aFw)]. Clinical trials studying baricitinib in COVID-19 have already begun in the US and in Italy [[224](#ref-jKRGxazA),[225](#ref-JCMhG5r9)]. Identification and targeting of further inflammatory markers that are relevant in SARS-CoV-2 infection may be of value for curtailing the inflammatory response and lung damage.

In addition to immunosuppressive treatments, which are most beneficial late in disease progression, much research is focused on identifying therapeutics for early-stage patients. For example, although studies of HCQ have not supported the early theory-driven interest in this antiviral treatment, alternative compounds with related mechanisms may still have potential. Hydroxyferroquine derivatives of HCQ have been described as a class of bioorganometallic compounds that exert antiviral effects with some selectivity for SARS-CoV-1 *in vitro* [[226](#ref-Cd5uMaAr)]. Future work could explore whether such compounds exert antiviral effects against SARS-CoV-2 and whether they would be safer for use in COVID-19. Another potential approach is the development of antivirals, which could be broad-spectrum, specific to coronaviruses, or targeted to SARS-CoV-2. Development of new antivirals is complicated by the fact that none have yet been approved for human coronaviruses. Intriguing new options are emerging, however. Beta-D-N4-hydroxycytidine (NHC) is an orally bioavailable ribonucleotide analog showing broad-spectrum activity against RNA viruses, which may inhibit SARS-CoV-2 replication *in vitro* and *in vivo* in mouse models of HCoVs [[227](#ref-TZleuwHX)]. A range of other antivirals are also in development. Development of antivirals will be further facilitated as research reveals more information about the interaction of SARS-CoV-2 with the host cell and host cell genome, mechanisms of viral replication, mechanisms of viral assembly, and mechanisms of viral release to other cells; this can allow researchers to target specific stages and structures of the viral life cycle. Finally, antibodies against viruses, also known as antiviral monoclonal antibodies, could be an alternative as well and are described in detail in an above section. The goal of antiviral antibodies is to neutralize viruses through either cell-killing activity or blocking of viral replication [[228](#ref-1FTnvyZlf)]. They may also engage the host immune response, encouraging the immune system to hone in on the virus. Given the cytokine storm that results from immune system activation in response to the virus, which has been implicated in worsening of the disease, an nAb may be preferable. Upcoming work may explore the specificity of nAbs for their target, mechanisms by which the nAbs impede the virus, and improvements to antibody structure that may enhance the ability of the antibody to block viral activity.

Some research is also investigating potential therapeutics and prophylactics that would interact with components of the innate immune response. For example, TLRs are pattern recognition receptors that recognize pathogen- and damage-associated molecular patterns and contribute to innate immune recognition and, more generally, promotion of both the innate and adaptive immune responses [[229](#ref-o6BQnEt7)]. In mouse models, poly(I:C) and CpG, which are agonists of Toll-like receptors TLR3 and TLR9, respectively, showed protective effects when administered prior to SARS-CoV-1 infection [[230](#ref-Ull2rQ5L)]. Therefore, TLR agonists hold some potential for broad-spectrum prophylaxis.

Given that a large number of clinical trials are currently in progress, more information about the potential of these and other therapeutics should become available over time. This information, combined with advances in understanding the molecular structure and viral pathogenesis of SARS-CoV-2, may lead to a more complete understanding of how the virus affects the human host and what strategies can improve outcomes. To date, investigations of potential therapeutics for COVID-19 have focused primarily on repurposing existing drugs. This approach is necessary given the urgency of the situation as well as the extensive time required for developing and testing new therapies. However, in the long-term, new drugs specific for treatment of COVID-19 may also enter development. Development of novel drugs is likely to be guided by what is known about the pathogenesis and molecular structure of SARS-CoV-2. For example, understanding the various structural components of SARS-CoV-2 may allow for the development of small molecule inhibitors of those components. Currently, crystal structures of the SARS-CoV-2 main protease have recently been resolved [[65](#ref-4Sja6dIz),[231](#ref-AJLaaguT)], and efforts are already in place to perform screens for small molecule inhibitors of the main protease, which have yielded potential hits [[65](#ref-4Sja6dIz)]. Much work remains to be done to determine further crystal structures of other viral components, understand the relative utility of targeting different viral components, perform additional small molecule inhibitor screens, and determine the safety and efficacy of the potential inhibitors. While still nascent, work in this area is promising. Over the longer term, this approach and others may lead to the development of novel therapeutics specifically for COVID-19 and SARS-CoV-2.

### Conclusions

Due to the large number of clinical trials currently under examination (Figure [2](#fig:ebm-trials)), not all candidates are examined here. Instead, this review seeks to provide an overview of the range of mechanisms that have been explored and to examine some prominent candidates in the context of the pathogenesis of and immune response to SARS-CoV-2. As more research becomes available, this review will be updated to include additional therapeutics that emerge and to include new findings that are released about those discussed here. While no therapeutics or vaccines were developed for SARS-CoV-1 or MERS-CoV, the current state of COVID-19 research suggests that the body of literature produced before and after the emergence of these viruses has prepared the biomedical community for a rapid response to novel HCoV like SARS-CoV-2. As the COVID-19 pandemic continues to be a topic of significant worldwide concern, more information is expected to become available about pharmaceutical mechanisms that can be used to combat this, and possibly other, HCoV. These advances therefore not only benefit the international community’s ability to respond to the current crisis, but are also likely to shape responses to future viral threats.

# Additional Items

## Competing Interests

|  |  |  |
| --- | --- | --- |
| Author | Competing Interests | Last Reviewed |
| Halie M. Rando | None | 2021-01-20 |
| Nils Wellhausen | None | 2020-11-03 |
| Soumita Ghosh | None | 2020-11-09 |
| Anna Ada Dattoli | None | 2020-03-26 |
| Fengling Hu | None | 2020-04-08 |
| Alexandra J. Lee | None | 2020-11-09 |
| Diane N. Rafizadeh | None | 2020-11-11 |
| James Brian Byrd | Funded by FastGrants to conduct a COVID-19-related clinical trial | 2020-11-12 |
| Yanjun Qi | None | 2020-07-09 |
| Yuchen Sun | None | 2020-11-11 |
| Jeffrey M. Field | None | 2020-11-12 |
| Marouen Ben Guebila | None | 2020-11-11 |
| Nafisa M. Jadavji | None | 2020-11-11 |
| Ronan Lordan | None | 2020-11-03 |
| Ashwin N. Skelly | None | 2020-11-11 |
| Christian Brueffer | Employee and shareholder of SAGA Diagnostics AB. | 2020-11-11 |
| Jinhui Wang | None | 2021-01-21 |
| Rishi Raj Goel | None | 2021-01-20 |
| YoSon Park | Now employed by Pfizer (subsequent to contributions to this project) | 2020-01-22 |
| COVID-19 Review Consortium | None | 2021-01-16 |
| Simina M. Boca | None | 2020-11-07 |
| Anthony Gitter | Filed a patent application with the Wisconsin Alumni Research Foundation related to classifying activated T cells | 2020-11-10 |
| Casey S. Greene | None | 2021-01-20 |

## Author Contributions

|  |  |
| --- | --- |
| Author | Contributions |
| Halie M. Rando | Project Administration, Writing - Original Draft, Writing - Review & Editing |
| Nils Wellhausen | Project Administration, Visualization, Writing - Original Draft, Writing - Review & Editing |
| Soumita Ghosh | Writing - Original Draft |
| Anna Ada Dattoli | Writing - Original Draft |
| Fengling Hu | Writing - Original Draft |
| Alexandra J. Lee | Writing - Original Draft, Writing - Review & Editing |
| Diane N. Rafizadeh | Project Administration, Writing - Original Draft, Writing - Review & Editing |
| James Brian Byrd | Writing - Original Draft |
| Yanjun Qi | Visualization |
| Yuchen Sun | Visualization |
| Jeffrey M. Field | Writing - Original Draft, Writing - Review & Editing |
| Marouen Ben Guebila | Writing - Original Draft |
| Nafisa M. Jadavji | Supervision, Writing - Review & Editing |
| Ronan Lordan | Project Administration, Writing - Original Draft, Writing - Review & Editing |
| Ashwin N. Skelly | Writing - Review & Editing |
| Christian Brueffer | Project Administration, Writing - Review & Editing |
| Jinhui Wang | Writing - Original Draft |
| Rishi Raj Goel | Writing - Review & Editing |
| YoSon Park | Writing - Review & Editing |
| COVID-19 Review Consortium | Project Administration |
| Simina M. Boca | Project Administration, Writing - Review & Editing |
| Anthony Gitter | Project Administration, Software, Visualization, Writing - Review & Editing |
| Casey S. Greene | Project Administration, Writing - Review & Editing |

## Acknowledgements

We thank Nick DeVito for assistance with the Evidence-Based Medicine Data Lab COVID-19 TrialsTracker data and Vincent Rubinetti and Daniel Himmelstein for feedback on and support with Manubot. We thank Yael Evelyn Marshall who contributed writing (original draft) as well as reviewing and editing of pieces of the text but who did not formally approve the manuscript, as well as Ronnie Russell, who contributed text to and helped develop the structure of the manuscript early in the writing process and Matthias Fax who helped with writing and editing text related to diagnostics. We are grateful to the following contributors for reviewing pieces of the text: Nadia Danilova, James Eberwine and Ipsita Krishnan.

# References

1. **Pathogenesis, Symptomatology, and Transmission of SARS-CoV-2 through analysis of Viral Genomics and Structure**   
Halie M. Rando, Adam L. MacLean, Alexandra J. Lee, Sandipan Ray, Vikas Bansal, Ashwin N. Skelly, Elizabeth Sell, John J. Dziak, Lamonica Shinholster, Lucy D’Agostino McGowan, … Casey S. Greene  
*arXiv* (2021-02-03) <https://arxiv.org/abs/2102.01521>

2. **Airborne Transmission of SARS-CoV-2**   
Michael Klompas, Meghan A. Baker, Chanu Rhee  
*JAMA* (2020-08-04) <https://doi.org/gg4ttq>   
DOI: [10.1001/jama.2020.12458](https://doi.org/10.1001/jama.2020.12458)

3. **Exaggerated risk of transmission of COVID-19 by fomites**   
Emanuel Goldman  
*The Lancet Infectious Diseases* (2020-08) <https://doi.org/gg6br7>   
DOI: [10.1016/s1473-3099(20)30561-2](https://doi.org/10.1016/s1473-3099(20)30561-2) · PMID: [32628907](https://www.ncbi.nlm.nih.gov/pubmed/32628907) · PMCID: [PMC7333993](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7333993)

4. **COVID-19 Data Repository**   
Center for Systems Science and Engineering at Johns Hopkins University  
*GitHub* <https://github.com/CSSEGISandData/COVID-19/tree/master/csse_covid_19_data/csse_covid_19_time_series>

5. **Three Emerging Coronaviruses in Two Decades**   
Jeannette Guarner  
*American Journal of Clinical Pathology* (2020-04) <https://doi.org/ggppq3>   
DOI: [10.1093/ajcp/aqaa029](https://doi.org/10.1093/ajcp/aqaa029) · PMID: [32053148](https://www.ncbi.nlm.nih.gov/pubmed/32053148) · PMCID: [PMC7109697](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7109697)

6. **SARS and MERS: recent insights into emerging coronaviruses**   
Emmie de Wit, Neeltje van Doremalen, Darryl Falzarano, Vincent J. Munster  
*Nature Reviews Microbiology* (2016-06-27) <https://doi.org/f8v5cv>   
DOI: [10.1038/nrmicro.2016.81](https://doi.org/10.1038/nrmicro.2016.81) · PMID: [27344959](https://www.ncbi.nlm.nih.gov/pubmed/27344959) · PMCID: [PMC7097822](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7097822)

7. **A Novel Coronavirus Genome Identified in a Cluster of Pneumonia Cases — Wuhan, China 2019−2020**   
Wenjie Tan, Xiang Zhao, Xuejun Ma, Wenling Wang, Peihua Niu, Wenbo Xu, George F. Gao, Guizhen Wu, MHC Key Laboratory of Biosafety, National Institute for Viral Disease Control and Prevention, China CDC, Beijing, China, Center for Biosafety Mega-Science, Chinese Academy of Sciences, Beijing, China  
*China CDC Weekly* (2020) <https://doi.org/gg8z47>   
DOI: [10.46234/ccdcw2020.017](https://doi.org/10.46234/ccdcw2020.017)

8. **Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding**   
Roujian Lu, Xiang Zhao, Juan Li, Peihua Niu, Bo Yang, Honglong Wu, Wenling Wang, Hao Song, Baoying Huang, Na Zhu, … Wenjie Tan  
*The Lancet* (2020-02) <https://doi.org/ggjr43>   
DOI: [10.1016/s0140-6736(20)30251-8](https://doi.org/10.1016/s0140-6736(20)30251-8)

9. **Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia**   
Ali M. Zaki, Sander van Boheemen, Theo M. Bestebroer, Albert D. M. E. Osterhaus, Ron A. M. Fouchier  
*New England Journal of Medicine* (2012-11-08) <https://doi.org/f4czx5>   
DOI: [10.1056/nejmoa1211721](https://doi.org/10.1056/nejmoa1211721) · PMID: [23075143](https://www.ncbi.nlm.nih.gov/pubmed/23075143)

10. **Causes of Death and Comorbidities in Patients with COVID-19**   
Sefer Elezkurtaj, Selina Greuel, Jana Ihlow, Edward Michaelis, Philip Bischoff, Catarina Alisa Kunze, Bruno Valentin Sinn, Manuela Gerhold, Kathrin Hauptmann, Barbara Ingold-Heppner, … David Horst  
*Cold Spring Harbor Laboratory* (2020-06-17) <https://doi.org/gg926j>   
DOI: [10.1101/2020.06.15.20131540](https://doi.org/10.1101/2020.06.15.20131540)

11. **Evidence-Based Medicine Data Lab COVID-19 TrialsTracker**   
Nick DeVito, Peter Inglesby  
*GitHub* (2020-03-29) <https://github.com/ebmdatalab/covid_trials_tracker-covid>   
DOI: [10.5281/zenodo.3732709](https://doi.org/10.5281/zenodo.3732709)

12. **Small Molecules vs Biologics | Drug Development Differences**   
Nuventra Pharma Sciences2525 Meridian Parkway, Suite 200 Durham  
*PK / PD and Clinical Pharmacology Consultants* (2020-05-13) <https://www.nuventra.com/resources/blog/small-molecules-versus-biologics/>

13. **Drug Discovery: A Historical Perspective**   
J. Drews  
*Science* (2000-03-17) <https://doi.org/d6bvp7>   
DOI: [10.1126/science.287.5460.1960](https://doi.org/10.1126/science.287.5460.1960) · PMID: [10720314](https://www.ncbi.nlm.nih.gov/pubmed/10720314)

14. **Introduction to modern virology**   
N. J. Dimmock, A. J. Easton, K. N. Leppard  
*Blackwell Pub* (2007)   
ISBN: [9781405136457](https://worldcat.org/isbn/9781405136457)

15. **Coronaviruses**   
Helena Jane Maier, Erica Bickerton, Paul Britton (editors)  
*Methods in Molecular Biology* (2015) <https://doi.org/ggqfqx>   
DOI: [10.1007/978-1-4939-2438-7](https://doi.org/10.1007/978-1-4939-2438-7) · PMID: [25870870](https://www.ncbi.nlm.nih.gov/pubmed/25870870) · ISBN: [9781493924370](https://worldcat.org/isbn/9781493924370)

16. **The potential chemical structure of anti‐SARS‐CoV‐2 RNA‐dependent RNA polymerase**   
Jrhau Lung, Yu‐Shih Lin, Yao‐Hsu Yang, Yu‐Lun Chou, Li‐Hsin Shu, Yu‐Ching Cheng, Hung Te Liu, Ching‐Yuan Wu  
*Journal of Medical Virology* (2020-03-18) <https://doi.org/ggp6fm>   
DOI: [10.1002/jmv.25761](https://doi.org/10.1002/jmv.25761) · PMID: [32167173](https://www.ncbi.nlm.nih.gov/pubmed/32167173)

17. **Broad-spectrum coronavirus antiviral drug discovery**   
Allison L. Totura, Sina Bavari  
*Expert Opinion on Drug Discovery* (2019-03-08) <https://doi.org/gg74z5>   
DOI: [10.1080/17460441.2019.1581171](https://doi.org/10.1080/17460441.2019.1581171) · PMID: [30849247](https://www.ncbi.nlm.nih.gov/pubmed/30849247) · PMCID: [PMC7103675](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7103675)

18. **Favipiravir**   
DrugBank  
(2020-06-12) <https://www.drugbank.ca/drugs/DB12466>

19. **In Vitro and In Vivo Activities of Anti-Influenza Virus Compound T-705**   
Y. Furuta, K. Takahashi, Y. Fukuda, M. Kuno, T. Kamiyama, K. Kozaki, N. Nomura, H. Egawa, S. Minami, Y. Watanabe, … K. Shiraki  
*Antimicrobial Agents and Chemotherapy* (2002-04) <https://doi.org/cndw7n>   
DOI: [10.1128/aac.46.4.977-981.2002](https://doi.org/10.1128/aac.46.4.977-981.2002) · PMID: [11897578](https://www.ncbi.nlm.nih.gov/pubmed/11897578) · PMCID: [PMC127093](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC127093)

20. **Efficacy of Orally Administered T-705 on Lethal Avian Influenza A (H5N1) Virus Infections in Mice**   
Robert W. Sidwell, Dale L. Barnard, Craig W. Day, Donald F. Smee, Kevin W. Bailey, Min-Hui Wong, John D. Morrey, Yousuke Furuta  
*Antimicrobial Agents and Chemotherapy* (2007-03) <https://doi.org/dm9xr2>   
DOI: [10.1128/aac.01051-06](https://doi.org/10.1128/aac.01051-06) · PMID: [17194832](https://www.ncbi.nlm.nih.gov/pubmed/17194832) · PMCID: [PMC1803113](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1803113)

21. **Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase**   
Yousuke FURUTA, Takashi KOMENO, Takaaki NAKAMURA  
*Proceedings of the Japan Academy, Series B* (2017) <https://doi.org/gbxcxw>   
DOI: [10.2183/pjab.93.027](https://doi.org/10.2183/pjab.93.027) · PMID: [28769016](https://www.ncbi.nlm.nih.gov/pubmed/28769016) · PMCID: [PMC5713175](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5713175)

22. **Mechanism of Action of T-705 against Influenza Virus**   
Yousuke Furuta, Kazumi Takahashi, Masako Kuno-Maekawa, Hidehiro Sangawa, Sayuri Uehara, Kyo Kozaki, Nobuhiko Nomura, Hiroyuki Egawa, Kimiyasu Shiraki  
*Antimicrobial Agents and Chemotherapy* (2005-03) <https://doi.org/dgbwdh>   
DOI: [10.1128/aac.49.3.981-986.2005](https://doi.org/10.1128/aac.49.3.981-986.2005) · PMID: [15728892](https://www.ncbi.nlm.nih.gov/pubmed/15728892) · PMCID: [PMC549233](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC549233)

23. **Activity of T-705 in a Hamster Model of Yellow Fever Virus Infection in Comparison with That of a Chemically Related Compound, T-1106**   
Justin G. Julander, Kristiina Shafer, Donald F. Smee, John D. Morrey, Yousuke Furuta  
*Antimicrobial Agents and Chemotherapy* (2009-01) <https://doi.org/brknds>   
DOI: [10.1128/aac.01074-08](https://doi.org/10.1128/aac.01074-08) · PMID: [18955536](https://www.ncbi.nlm.nih.gov/pubmed/18955536) · PMCID: [PMC2612161](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2612161)

24. **In Vitro and In Vivo Activities of T-705 against Arenavirus and Bunyavirus Infections**   
Brian B. Gowen, Min-Hui Wong, Kie-Hoon Jung, Andrew B. Sanders, Michelle Mendenhall, Kevin W. Bailey, Yousuke Furuta, Robert W. Sidwell  
*Antimicrobial Agents and Chemotherapy* (2007-09) <https://doi.org/d98c87>   
DOI: [10.1128/aac.00356-07](https://doi.org/10.1128/aac.00356-07) · PMID: [17606691](https://www.ncbi.nlm.nih.gov/pubmed/17606691) · PMCID: [PMC2043187](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2043187)

25. **Favipiravir (T-705) inhibits in vitro norovirus replication**   
J. Rocha-Pereira, D. Jochmans, K. Dallmeier, P. Leyssen, M. S. J. Nascimento, J. Neyts  
*Biochemical and Biophysical Research Communications* (2012-08) <https://doi.org/f369j7>   
DOI: [10.1016/j.bbrc.2012.07.034](https://doi.org/10.1016/j.bbrc.2012.07.034) · PMID: [22809499](https://www.ncbi.nlm.nih.gov/pubmed/22809499)

26. **T-705 (Favipiravir) Inhibition of Arenavirus Replication in Cell Culture**   
Michelle Mendenhall, Andrew Russell, Terry Juelich, Emily L. Messina, Donald F. Smee, Alexander N. Freiberg, Michael R. Holbrook, Yousuke Furuta, Juan-Carlos de la Torre, Jack H. Nunberg, Brian B. Gowen  
*Antimicrobial Agents and Chemotherapy* (2011-02) <https://doi.org/cppwsc>   
DOI: [10.1128/aac.01219-10](https://doi.org/10.1128/aac.01219-10) · PMID: [21115797](https://www.ncbi.nlm.nih.gov/pubmed/21115797) · PMCID: [PMC3028760](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3028760)

27. **The evolution of nucleoside analogue antivirals: A review for chemists and non-chemists. Part 1: Early structural modifications to the nucleoside scaffold**   
Katherine L. Seley-Radtke, Mary K. Yates  
*Antiviral Research* (2018-06) <https://doi.org/gdpn35>   
DOI: [10.1016/j.antiviral.2018.04.004](https://doi.org/10.1016/j.antiviral.2018.04.004) · PMID: [29649496](https://www.ncbi.nlm.nih.gov/pubmed/29649496) · PMCID: [PMC6396324](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6396324)

28. **The Ambiguous Base-Pairing and High Substrate Efficiency of T-705 (Favipiravir) Ribofuranosyl 5′-Triphosphate towards Influenza A Virus Polymerase**   
Zhinan Jin, Lucas K. Smith, Vivek K. Rajwanshi, Baek Kim, Jerome Deval  
*PLoS ONE* (2013-07-10) <https://doi.org/f5br92>   
DOI: [10.1371/journal.pone.0068347](https://doi.org/10.1371/journal.pone.0068347) · PMID: [23874596](https://www.ncbi.nlm.nih.gov/pubmed/23874596) · PMCID: [PMC3707847](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3707847)

29. **Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study**   
Qingxian Cai, Minghui Yang, Dongjing Liu, Jun Chen, Dan Shu, Junxia Xia, Xuejiao Liao, Yuanbo Gu, Qiue Cai, Yang Yang, … Lei Liu  
*Engineering* (2020-10) <https://doi.org/ggpprd>   
DOI: [10.1016/j.eng.2020.03.007](https://doi.org/10.1016/j.eng.2020.03.007) · PMID: [32346491](https://www.ncbi.nlm.nih.gov/pubmed/32346491)

30. **Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results**   
WHO Solidarity Trial Consortium  
*New England Journal of Medicine* (2020-12-02) <https://doi.org/ghnhnw>   
DOI: [10.1056/nejmoa2023184](https://doi.org/10.1056/nejmoa2023184) · PMID: [33264556](https://www.ncbi.nlm.nih.gov/pubmed/33264556) · PMCID: [PMC7727327](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7727327)

31. **Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial**   
Peter W Horby, Marion Mafham, Jennifer L Bell, Louise Linsell, Natalie Staplin, Jonathan Emberson, Adrian Palfreeman, Jason Raw, Einas Elmahi, Benjamin Prudon, … Martin J Landray  
*The Lancet* (2020-10) <https://doi.org/fnx2>   
DOI: [10.1016/s0140-6736(20)32013-4](https://doi.org/10.1016/s0140-6736(20)32013-4) · PMID: [33031764](https://www.ncbi.nlm.nih.gov/pubmed/33031764) · PMCID: [PMC7535623](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7535623)

32. **A Large, Simple Trial Leading to Complex Questions**   
David P. Harrington, Lindsey R. Baden, Joseph W. Hogan  
*New England Journal of Medicine* (2020-12-02) <https://doi.org/ghnhnx>   
DOI: [10.1056/nejme2034294](https://doi.org/10.1056/nejme2034294) · PMID: [33264557](https://www.ncbi.nlm.nih.gov/pubmed/33264557) · PMCID: [PMC7727323](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7727323)

33. **Retracted coronavirus (COVID-19) papers**   
Retraction Watch  
(2020-04-29) <https://retractionwatch.com/retracted-coronavirus-covid-19-papers/>

34. **Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: An Exploratory Randomized, Controlled Trial**   
Yan Lou, Lin Liu, Hangping Yao, Xingjiang Hu, Junwei Su, Kaijin Xu, Rui Luo, Xi Yang, Lingjuan He, Xiaoyang Lu, … Yunqing Qiu  
*European Journal of Pharmaceutical Sciences* (2021-02) <https://doi.org/ghx88n>   
DOI: [10.1016/j.ejps.2020.105631](https://doi.org/10.1016/j.ejps.2020.105631) · PMID: [33115675](https://www.ncbi.nlm.nih.gov/pubmed/33115675) · PMCID: [PMC7585719](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7585719)

35. **Efficacy of favipiravir in COVID-19 treatment: a multi-center randomized study**   
Hany M. Dabbous, Sherief Abd-Elsalam, Manal H. El-Sayed, Ahmed F. Sherief, Fatma F. S. Ebeid, Mohamed Samir Abd El Ghafar, Shaimaa Soliman, Mohamed Elbahnasawy, Rehab Badawi, Mohamed Awad Tageldin  
*Archives of Virology* (2021-01-25) <https://doi.org/ghx874>   
DOI: [10.1007/s00705-021-04956-9](https://doi.org/10.1007/s00705-021-04956-9) · PMID: [33492523](https://www.ncbi.nlm.nih.gov/pubmed/33492523) · PMCID: [PMC7829645](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7829645)

36. **AVIFAVIR for Treatment of Patients With Moderate Coronavirus Disease 2019 (COVID-19): Interim Results of a Phase II/III Multicenter Randomized Clinical Trial**   
Andrey A Ivashchenko, Kirill A Dmitriev, Natalia V Vostokova, Valeria N Azarova, Andrew A Blinow, Alina N Egorova, Ivan G Gordeev, Alexey P Ilin, Ruben N Karapetian, Dmitry V Kravchenko, … Alexandre V Ivachtchenko  
*Clinical Infectious Diseases* (2020-08-09) <https://doi.org/ghx9c2>   
DOI: [10.1093/cid/ciaa1176](https://doi.org/10.1093/cid/ciaa1176) · PMID: [32770240](https://www.ncbi.nlm.nih.gov/pubmed/32770240) · PMCID: [PMC7454388](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7454388)

37. **A review of the safety of favipiravir – a potential treatment in the COVID-19 pandemic?**   
Victoria Pilkington, Toby Pepperrell, Andrew Hill  
*Journal of Virus Eradication* (2020-04) <https://doi.org/ftgm>   
DOI: [10.1016/s2055-6640(20)30016-9](https://doi.org/10.1016/s2055-6640(20)30016-9) · PMID: [32405421](https://www.ncbi.nlm.nih.gov/pubmed/32405421) · PMCID: [PMC7331506](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7331506)

38. **Remdesivir EUA Letter of Authorization**   
Denise M Hinton  
(2020-05-01) <https://www.fda.gov/media/137564/download>

39. **A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe COVID-19**   
Gilead Sciences  
*clinicaltrials.gov* (2020-12-15) <https://clinicaltrials.gov/ct2/show/NCT04292899>

40. **A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults**   
National Institute of Allergy and Infectious Diseases (NIAID)  
*clinicaltrials.gov* (2020-12-05) <https://clinicaltrials.gov/ct2/show/NCT04280705>

41. **Remdesivir for the Treatment of Covid-19 — Final Report**   
John H. Beigel, Kay M. Tomashek, Lori E. Dodd, Aneesh K. Mehta, Barry S. Zingman, Andre C. Kalil, Elizabeth Hohmann, Helen Y. Chu, Annie Luetkemeyer, Susan Kline, … H. Clifford Lane  
*New England Journal of Medicine* (2020-11-05) <https://doi.org/dwkd>   
DOI: [10.1056/nejmoa2007764](https://doi.org/10.1056/nejmoa2007764) · PMID: [32445440](https://www.ncbi.nlm.nih.gov/pubmed/32445440) · PMCID: [PMC7262788](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7262788)

42. **Compassionate Use of Remdesivir for Patients with Severe Covid-19**   
Jonathan Grein, Norio Ohmagari, Daniel Shin, George Diaz, Erika Asperges, Antonella Castagna, Torsten Feldt, Gary Green, Margaret L. Green, François-Xavier Lescure, … Timothy Flanigan  
*New England Journal of Medicine* (2020-06-11) <https://doi.org/ggrm99>   
DOI: [10.1056/nejmoa2007016](https://doi.org/10.1056/nejmoa2007016) · PMID: [32275812](https://www.ncbi.nlm.nih.gov/pubmed/32275812) · PMCID: [PMC7169476](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7169476)

43. **The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus**   
Calvin J. Gordon, Egor P. Tchesnokov, Joy Y. Feng, Danielle P. Porter, Matthias Götte  
*Journal of Biological Chemistry* (2020-04) <https://doi.org/ggqm6x>   
DOI: [10.1074/jbc.ac120.013056](https://doi.org/10.1074/jbc.ac120.013056) · PMID: [32094225](https://www.ncbi.nlm.nih.gov/pubmed/32094225)

44. **Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease**   
Maria L. Agostini, Erica L. Andres, Amy C. Sims, Rachel L. Graham, Timothy P. Sheahan, Xiaotao Lu, Everett Clinton Smith, James Brett Case, Joy Y. Feng, Robert Jordan, … Mark R. Denison  
*mBio* (2018-03-06) <https://doi.org/gc45v6>   
DOI: [10.1128/mbio.00221-18](https://doi.org/10.1128/mbio.00221-18) · PMID: [29511076](https://www.ncbi.nlm.nih.gov/pubmed/29511076) · PMCID: [PMC5844999](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5844999)

45. **Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro**   
Manli Wang, Ruiyuan Cao, Leike Zhang, Xinglou Yang, Jia Liu, Mingyue Xu, Zhengli Shi, Zhihong Hu, Wu Zhong, Gengfu Xiao  
*Cell Research* (2020-02-04) <https://doi.org/ggkbsg>   
DOI: [10.1038/s41422-020-0282-0](https://doi.org/10.1038/s41422-020-0282-0) · PMID: [32020029](https://www.ncbi.nlm.nih.gov/pubmed/32020029) · PMCID: [PMC7054408](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7054408)

46. **A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics**   
Sabue Mulangu, Lori E. Dodd, Richard T. Davey, Olivier Tshiani Mbaya, Michael Proschan, Daniel Mukadi, Mariano Lusakibanza Manzo, Didier Nzolo, Antoine Tshomba Oloma, Augustin Ibanda, … the PALM Writing Group  
*New England Journal of Medicine* (2019-12-12) <https://doi.org/ggqmx4>   
DOI: [10.1056/nejmoa1910993](https://doi.org/10.1056/nejmoa1910993) · PMID: [31774950](https://www.ncbi.nlm.nih.gov/pubmed/31774950)

47. **Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses**   
Timothy P. Sheahan, Amy C. Sims, Rachel L. Graham, Vineet D. Menachery, Lisa E. Gralinski, James B. Case, Sarah R. Leist, Krzysztof Pyrc, Joy Y. Feng, Iva Trantcheva, … Ralph S. Baric  
*Science Translational Medicine* (2017-06-28) <https://doi.org/gc3grb>   
DOI: [10.1126/scitranslmed.aal3653](https://doi.org/10.1126/scitranslmed.aal3653) · PMID: [28659436](https://www.ncbi.nlm.nih.gov/pubmed/28659436) · PMCID: [PMC5567817](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5567817)

48. **Did an experimental drug help a U.S. coronavirus patient?**   
Jon Cohen  
*Science* (2020-03-13) <https://doi.org/ggqm62>   
DOI: [10.1126/science.abb7243](https://doi.org/10.1126/science.abb7243)

49. **First 12 patients with coronavirus disease 2019 (COVID-19) in the United States**   
Stephanie A. Kujawski, Karen K Wong, Jennifer P. Collins, Lauren Epstein, Marie E. Killerby, Claire M. Midgley, Glen R. Abedi, N. Seema Ahmed, Olivia Almendares, Francisco N. Alvarez, … The COVID-19 Investigation Team  
*Cold Spring Harbor Laboratory* (2020-03-12) <https://doi.org/ggqm6z>   
DOI: [10.1101/2020.03.09.20032896](https://doi.org/10.1101/2020.03.09.20032896)

50. **First Case of 2019 Novel Coronavirus in the United States**   
Michelle L. Holshue, Chas DeBolt, Scott Lindquist, Kathy H. Lofy, John Wiesman, Hollianne Bruce, Christopher Spitters, Keith Ericson, Sara Wilkerson, Ahmet Tural, … Satish K. Pillai  
*New England Journal of Medicine* (2020-03-05) <https://doi.org/ggjvr6>   
DOI: [10.1056/nejmoa2001191](https://doi.org/10.1056/nejmoa2001191) · PMID: [32004427](https://www.ncbi.nlm.nih.gov/pubmed/32004427) · PMCID: [PMC7092802](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7092802)

51. **Remdesivir for 5 or 10 Days in Patients with Severe Covid-19**   
Jason D. Goldman, David C. B. Lye, David S. Hui, Kristen M. Marks, Raffaele Bruno, Rocio Montejano, Christoph D. Spinner, Massimo Galli, Mi-Young Ahn, Ronald G. Nahass, … Aruna Subramanian  
*New England Journal of Medicine* (2020-11-05) <https://doi.org/ggz7qv>   
DOI: [10.1056/nejmoa2015301](https://doi.org/10.1056/nejmoa2015301) · PMID: [32459919](https://www.ncbi.nlm.nih.gov/pubmed/32459919) · PMCID: [PMC7377062](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7377062)

52. **A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate COVID-19 Compared to Standard of Care Treatment**   
Gilead Sciences  
*clinicaltrials.gov* (2021-01-21) <https://clinicaltrials.gov/ct2/show/NCT04292730>

53. **Multi-centre, adaptive, randomized trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults**   
EU Clinical Trials Register  
(2020-03-09) <https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-000936-23/FR>

54. **A Trial of Remdesivir in Adults With Mild and Moderate COVID-19 - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04252664>

55. **A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients With Severe COVID-19.**   
Bin Cao  
*clinicaltrials.gov* (2020-04-13) <https://clinicaltrials.gov/ct2/show/NCT04257656>

56. **FDA Approves First Treatment for COVID-19**   
Office of the Commissioner  
*FDA* (2020-10-22) <https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19>

57. **Gilead Sciences Statement on the Solidarity Trial** <https://www.gilead.com/news-and-press/company-statements/gilead-sciences-statement-on-the-solidarity-trial>

58. **Conflicting results on the efficacy of remdesivir in hospitalized Covid-19 patients: *comment on the Adaptive Covid-19 Treatment Trial***   
Leonarda Galiuto, Carlo Patrono  
*European Heart Journal* (2020-12-07) <https://doi.org/ghp4kw>   
DOI: [10.1093/eurheartj/ehaa934](https://doi.org/10.1093/eurheartj/ehaa934) · PMID: [33306101](https://www.ncbi.nlm.nih.gov/pubmed/33306101) · PMCID: [PMC7799042](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7799042)

59. **The “very, very bad look” of remdesivir, the first FDA-approved COVID-19 drug**   
Jon Cohen, Kai KupferschmidtOct. 28, 2020, 7:05 Pm  
*Science | AAAS* (2020-10-28) <https://www.sciencemag.org/news/2020/10/very-very-bad-look-remdesivir-first-fda-approved-covid-19-drug>

60. **Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19**   
Christoph D. Spinner, Robert L. Gottlieb, Gerard J. Criner, José Ramón Arribas López, Anna Maria Cattelan, Alex Soriano Viladomiu, Onyema Ogbuagu, Prashant Malhotra, Kathleen M. Mullane, Antonella Castagna, … for the GS-US-540-5774 Investigators  
*JAMA* (2020-09-15) <https://doi.org/ghhz6g>   
DOI: [10.1001/jama.2020.16349](https://doi.org/10.1001/jama.2020.16349) · PMID: [32821939](https://www.ncbi.nlm.nih.gov/pubmed/32821939) · PMCID: [PMC7442954](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7442954)

61. **Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19**   
Andre C. Kalil, Thomas F. Patterson, Aneesh K. Mehta, Kay M. Tomashek, Cameron R. Wolfe, Varduhi Ghazaryan, Vincent C. Marconi, Guillermo M. Ruiz-Palacios, Lanny Hsieh, Susan Kline, … John H. Beigel  
*New England Journal of Medicine* (2020-12-11) <https://doi.org/ghpbd2>   
DOI: [10.1056/nejmoa2031994](https://doi.org/10.1056/nejmoa2031994) · PMID: [33306283](https://www.ncbi.nlm.nih.gov/pubmed/33306283) · PMCID: [PMC7745180](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7745180)

62. **Proteases Essential for Human Influenza Virus Entry into Cells and Their Inhibitors as Potential Therapeutic Agents**   
Hiroshi Kido, Yuushi Okumura, Hiroshi Yamada, Trong Quang Le, Mihiro Yano  
*Current Pharmaceutical Design* (2007-02-01) <https://doi.org/bts3xp>   
DOI: [10.2174/138161207780162971](https://doi.org/10.2174/138161207780162971) · PMID: [17311557](https://www.ncbi.nlm.nih.gov/pubmed/17311557)

63. **Protease inhibitors targeting coronavirus and filovirus entry**   
Yanchen Zhou, Punitha Vedantham, Kai Lu, Juliet Agudelo, Ricardo Carrion, Jerritt W. Nunneley, Dale Barnard, Stefan Pöhlmann, James H. McKerrow, Adam R. Renslo, Graham Simmons  
*Antiviral Research* (2015-04) <https://doi.org/ggr984>   
DOI: [10.1016/j.antiviral.2015.01.011](https://doi.org/10.1016/j.antiviral.2015.01.011) · PMID: [25666761](https://www.ncbi.nlm.nih.gov/pubmed/25666761) · PMCID: [PMC4774534](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4774534)

64. **SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor**   
Markus Hoffmann, Hannah Kleine-Weber, Simon Schroeder, Nadine Krüger, Tanja Herrler, Sandra Erichsen, Tobias S. Schiergens, Georg Herrler, Nai-Huei Wu, Andreas Nitsche, … Stefan Pöhlmann  
*Cell* (2020-04) <https://doi.org/ggnq74>   
DOI: [10.1016/j.cell.2020.02.052](https://doi.org/10.1016/j.cell.2020.02.052) · PMID: [32142651](https://www.ncbi.nlm.nih.gov/pubmed/32142651) · PMCID: [PMC7102627](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102627)

65. **Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors**   
Zhenming Jin, Xiaoyu Du, Yechun Xu, Yongqiang Deng, Meiqin Liu, Yao Zhao, Bing Zhang, Xiaofeng Li, Leike Zhang, Chao Peng, … Haitao Yang  
*Nature* (2020-04-09) <https://doi.org/ggrp42>   
DOI: [10.1038/s41586-020-2223-y](https://doi.org/10.1038/s41586-020-2223-y) · PMID: [32272481](https://www.ncbi.nlm.nih.gov/pubmed/32272481)

66. **Design of Wide-Spectrum Inhibitors Targeting Coronavirus Main Proteases**   
Haitao Yang, Weiqing Xie, Xiaoyu Xue, Kailin Yang, Jing Ma, Wenxue Liang, Qi Zhao, Zhe Zhou, Duanqing Pei, John Ziebuhr, … Zihe Rao  
*PLoS Biology* (2005-09-06) <https://doi.org/bcm9k7>   
DOI: [10.1371/journal.pbio.0030324](https://doi.org/10.1371/journal.pbio.0030324) · PMID: [16128623](https://www.ncbi.nlm.nih.gov/pubmed/16128623) · PMCID: [PMC1197287](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1197287)

67. **The newly emerged SARS-Like coronavirus HCoV-EMC also has an “Achilles’ heel”: current effective inhibitor targeting a 3C-like protease**   
Zhilin Ren, Liming Yan, Ning Zhang, Yu Guo, Cheng Yang, Zhiyong Lou, Zihe Rao  
*Protein & Cell* (2013-04-03) <https://doi.org/ggr7vh>   
DOI: [10.1007/s13238-013-2841-3](https://doi.org/10.1007/s13238-013-2841-3) · PMID: [23549610](https://www.ncbi.nlm.nih.gov/pubmed/23549610) · PMCID: [PMC4875521](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4875521)

68. **Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors**   
Linlin Zhang, Daizong Lin, Xinyuanyuan Sun, Ute Curth, Christian Drosten, Lucie Sauerhering, Stephan Becker, Katharina Rox, Rolf Hilgenfeld  
*Science* (2020-04-24) <https://doi.org/ggp9sb>   
DOI: [10.1126/science.abb3405](https://doi.org/10.1126/science.abb3405) · PMID: [32198291](https://www.ncbi.nlm.nih.gov/pubmed/32198291) · PMCID: [PMC7164518](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164518)

69. **Ebselen, a promising antioxidant drug: mechanisms of action and targets of biological pathways**   
Gajendra Kumar Azad, Raghuvir S. Tomar  
*Molecular Biology Reports* (2014-05-28) <https://doi.org/f6cnq3>   
DOI: [10.1007/s11033-014-3417-x](https://doi.org/10.1007/s11033-014-3417-x) · PMID: [24867080](https://www.ncbi.nlm.nih.gov/pubmed/24867080)

70. **Safety and efficacy of ebselen for the prevention of noise-induced hearing loss: a randomised, double-blind, placebo-controlled, phase 2 trial**   
Jonathan Kil, Edward Lobarinas, Christopher Spankovich, Scott K Griffiths, Patrick J Antonelli, Eric D Lynch, Colleen G Le Prell  
*The Lancet* (2017-09) <https://doi.org/gbwnbv>   
DOI: [10.1016/s0140-6736(17)31791-9](https://doi.org/10.1016/s0140-6736(17)31791-9)

71. **Potential therapeutic use of ebselen for COVID-19 and other respiratory viral infections**   
Helmut Sies, Michael J. Parnham  
*Free Radical Biology and Medicine* (2020-08) <https://doi.org/ghdx7s>   
DOI: [10.1016/j.freeradbiomed.2020.06.032](https://doi.org/10.1016/j.freeradbiomed.2020.06.032) · PMID: [32598985](https://www.ncbi.nlm.nih.gov/pubmed/32598985) · PMCID: [PMC7319625](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7319625)

72. **Selenium Deficiency Is Associated with Mortality Risk from COVID-19**   
Arash Moghaddam, Raban Arved Heller, Qian Sun, Julian Seelig, Asan Cherkezov, Linda Seibert, Julian Hackler, Petra Seemann, Joachim Diegmann, Maximilian Pilz, … Lutz Schomburg  
*Nutrients* (2020-07-16) <https://doi.org/gg5kbc>   
DOI: [10.3390/nu12072098](https://doi.org/10.3390/nu12072098) · PMID: [32708526](https://www.ncbi.nlm.nih.gov/pubmed/32708526) · PMCID: [PMC7400921](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7400921)

73. **Selenium and viral infection: are there lessons for COVID-19?**   
Giovanna Bermano, Catherine Méplan, Derry K. Mercer, John E. Hesketh  
*British Journal of Nutrition* (2020-08-06) <https://doi.org/ghdx7w>   
DOI: [10.1017/s0007114520003128](https://doi.org/10.1017/s0007114520003128) · PMID: [32758306](https://www.ncbi.nlm.nih.gov/pubmed/32758306) · PMCID: [PMC7503044](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7503044)

74. **Selenium and selenoproteins in viral infection with potential relevance to COVID-19**   
Jinsong Zhang, Ramy Saad, Ethan Will Taylor, Margaret P. Rayman  
*Redox Biology* (2020-10) <https://doi.org/ghdx7t>   
DOI: [10.1016/j.redox.2020.101715](https://doi.org/10.1016/j.redox.2020.101715) · PMID: [32992282](https://www.ncbi.nlm.nih.gov/pubmed/32992282) · PMCID: [PMC7481318](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7481318)

75. **FDA Clears SPI’s Ebselen For Phase II COVID-19 Trials**   
Contract Pharma  
<https://www.contractpharma.com/contents/view_breaking-news/2020-08-31/fda-clears-spis-ebselen-for-phase-ii-covid-19-trials/>

76. **A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose Escalation Study to Evaluate the Safety and Efficacy of SPI-1005 in Moderate COVID-19 Patients**   
Sound Pharmaceuticals, Incorporated  
*clinicaltrials.gov* (2020-11-06) <https://clinicaltrials.gov/ct2/show/NCT04484025>

77. **A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose Escalation Study to Evaluate the Safety and Efficacy of SPI-1005 in Severe COVID-19 Patients**   
Sound Pharmaceuticals, Incorporated  
*clinicaltrials.gov* (2020-11-06) <https://clinicaltrials.gov/ct2/show/NCT04483973>

78. **Target discovery of ebselen with a biotinylated probe**   
Zhenzhen Chen, Zhongyao Jiang, Nan Chen, Qian Shi, Lili Tong, Fanpeng Kong, Xiufen Cheng, Hao Chen, Chu Wang, Bo Tang  
*Chemical Communications* (2018) <https://doi.org/ggrtcm>   
DOI: [10.1039/c8cc04258f](https://doi.org/10.1039/c8cc04258f) · PMID: [30091742](https://www.ncbi.nlm.nih.gov/pubmed/30091742)

79. **Curing a viral infection by targeting the host: The example of cyclophilin inhibitors**   
Kai Lin, Philippe Gallay  
*Antiviral Research* (2013-07) <https://doi.org/f4237c>   
DOI: [10.1016/j.antiviral.2013.03.020](https://doi.org/10.1016/j.antiviral.2013.03.020) · PMID: [23578729](https://www.ncbi.nlm.nih.gov/pubmed/23578729) · PMCID: [PMC4332838](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4332838)

80. **Lisinopril - Drug Usage Statistics**   
ClinCalc DrugStats Database  
<https://clincalc.com/DrugStats/Drugs/Lisinopril>

81. **Hypertension Hot Potato — Anatomy of the Angiotensin-Receptor Blocker Recalls**   
J. Brian Byrd, Glenn M. Chertow, Vivek Bhalla  
*New England Journal of Medicine* (2019-04-25) <https://doi.org/ggvc7g>   
DOI: [10.1056/nejmp1901657](https://doi.org/10.1056/nejmp1901657) · PMID: [30865819](https://www.ncbi.nlm.nih.gov/pubmed/30865819) · PMCID: [PMC7066505](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7066505)

82. **Hypertension, the renin–angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19**   
Reinhold Kreutz, Engi Abd El-Hady Algharably, Michel Azizi, Piotr Dobrowolski, Tomasz Guzik, Andrzej Januszewicz, Alexandre Persu, Aleksander Prejbisz, Thomas Günther Riemer, Ji-Guang Wang, Michel Burnier  
*Cardiovascular Research* (2020-08-01) <https://doi.org/ggtwpj>   
DOI: [10.1093/cvr/cvaa097](https://doi.org/10.1093/cvr/cvaa097) · PMID: [32293003](https://www.ncbi.nlm.nih.gov/pubmed/32293003) · PMCID: [PMC7184480](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7184480)

83. **Angiotensin converting enzyme 2 activity and human atrial fibrillation: increased plasma angiotensin converting enzyme 2 activity is associated with atrial fibrillation and more advanced left atrial structural remodelling**   
Tomos E. Walters, Jonathan M. Kalman, Sheila K. Patel, Megan Mearns, Elena Velkoska, Louise M. Burrell  
*Europace* (2016-10-12) <https://doi.org/gbt2jw>   
DOI: [10.1093/europace/euw246](https://doi.org/10.1093/europace/euw246) · PMID: [27738071](https://www.ncbi.nlm.nih.gov/pubmed/27738071)

84. **Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19**   
Mandeep R. Mehra, Sapan S. Desai, SreyRam Kuy, Timothy D. Henry, Amit N. Patel  
*New England Journal of Medicine* (2020-06-18) <https://doi.org/ggtp6v>   
DOI: [10.1056/nejmoa2007621](https://doi.org/10.1056/nejmoa2007621) · PMID: [32356626](https://www.ncbi.nlm.nih.gov/pubmed/32356626) · PMCID: [PMC7206931](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7206931)

85. **Response by Cohen et al to Letter Regarding Article, “Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19”**   
Jordana B. Cohen, Thomas C. Hanff, Andrew M. South, Matthew A. Sparks, Swapnil Hiremath, Adam P. Bress, J. Brian Byrd, Julio A. Chirinos  
*Circulation Research* (2020-06-05) <https://doi.org/gg3xsg>   
DOI: [10.1161/circresaha.120.317205](https://doi.org/10.1161/circresaha.120.317205) · PMID: [32496917](https://www.ncbi.nlm.nih.gov/pubmed/32496917) · PMCID: [PMC7265880](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7265880)

86. **Sound Science before Quick Judgement Regarding RAS Blockade in COVID-19**   
Matthew A. Sparks, Andrew South, Paul Welling, J. Matt Luther, Jordana Cohen, James Brian Byrd, Louise M. Burrell, Daniel Batlle, Laurie Tomlinson, Vivek Bhalla, … Swapnil Hiremath  
*Clinical Journal of the American Society of Nephrology* (2020-05-07) <https://doi.org/ggq8gn>   
DOI: [10.2215/cjn.03530320](https://doi.org/10.2215/cjn.03530320) · PMID: [32220930](https://www.ncbi.nlm.nih.gov/pubmed/32220930) · PMCID: [PMC7269218](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7269218)

87. **Elimination or Prolongation of ACE Inhibitors and ARB in Coronavirus Disease 2019 - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04338009>

88. **Stopping ACE-inhibitors in COVID-19 - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04353596>

89. **Losartan for Patients With COVID-19 Not Requiring Hospitalization - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04311177>

90. **Losartan for Patients With COVID-19 Requiring Hospitalization - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04312009>

91. **The CORONAvirus Disease 2019 Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker InvestigatiON (CORONACION) Randomized Clinical Trial**   
Prof John William McEvoy  
*clinicaltrials.gov* (2020-06-26) <https://clinicaltrials.gov/ct2/show/NCT04330300>

92. **Ramipril for the Treatment of COVID-19 - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04366050>

93. **The Coronavirus Conundrum: ACE2 and Hypertension Edition**   
Matthew Sparks, Swapnil Hiremath  
*NephJC* <http://www.nephjc.com/news/covidace2>

94. **Lysosomotropic agents as HCV entry inhibitors**   
Usman A Ashfaq, Tariq Javed, Sidra Rehman, Zafar Nawaz, Sheikh Riazuddin  
*Virology Journal* (2011-04-12) <https://doi.org/dr5g4m>   
DOI: [10.1186/1743-422x-8-163](https://doi.org/10.1186/1743-422x-8-163) · PMID: [21481279](https://www.ncbi.nlm.nih.gov/pubmed/21481279) · PMCID: [PMC3090357](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3090357)

95. **New concepts in antimalarial use and mode of action in dermatology**   
Sunil Kalia, Jan P Dutz  
*Dermatologic Therapy* (2007-07) <https://doi.org/fv69cb>   
DOI: [10.1111/j.1529-8019.2007.00131.x](https://doi.org/10.1111/j.1529-8019.2007.00131.x) · PMID: [17970883](https://www.ncbi.nlm.nih.gov/pubmed/17970883) · PMCID: [PMC7163426](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7163426)

96. **Chloroquine is a potent inhibitor of SARS coronavirus infection and spread**   
Martin J Vincent, Eric Bergeron, Suzanne Benjannet, Bobbie R Erickson, Pierre E Rollin, Thomas G Ksiazek, Nabil G Seidah, Stuart T Nichol  
*Virology Journal* (2005) <https://doi.org/dvbds4>   
DOI: [10.1186/1743-422x-2-69](https://doi.org/10.1186/1743-422x-2-69) · PMID: [16115318](https://www.ncbi.nlm.nih.gov/pubmed/16115318) · PMCID: [PMC1232869](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1232869)

97. **In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)**   
Xueting Yao, Fei Ye, Miao Zhang, Cheng Cui, Baoying Huang, Peihua Niu, Xu Liu, Li Zhao, Erdan Dong, Chunli Song, … Dongyang Liu  
*Clinical Infectious Diseases* (2020-08-01) <https://doi.org/ggpx7z>   
DOI: [10.1093/cid/ciaa237](https://doi.org/10.1093/cid/ciaa237) · PMID: [32150618](https://www.ncbi.nlm.nih.gov/pubmed/32150618) · PMCID: [PMC7108130](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7108130)

98. **Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19**   
Yan Zhang, Meng Xiao, Shulan Zhang, Peng Xia, Wei Cao, Wei Jiang, Huan Chen, Xin Ding, Hua Zhao, Hongmin Zhang, … Shuyang Zhang  
*New England Journal of Medicine* (2020-04-23) <https://doi.org/ggrgz7>   
DOI: [10.1056/nejmc2007575](https://doi.org/10.1056/nejmc2007575) · PMID: [32268022](https://www.ncbi.nlm.nih.gov/pubmed/32268022) · PMCID: [PMC7161262](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7161262)

99. **Mechanism of Action of Hydroxychloroquine in the Antiphospholipid Syndrome**   
Nadine Müller-Calleja, Davit Manukyan, Wolfram Ruf, Karl Lackner  
*Blood* (2016-12-02) <https://doi.org/ggrm82>   
DOI: [10.1182/blood.v128.22.5023.5023](https://doi.org/10.1182/blood.v128.22.5023.5023)

100. **14th International Congress on Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome Treatment Trends**   
Doruk Erkan, Cassyanne L. Aguiar, Danieli Andrade, Hannah Cohen, Maria J. Cuadrado, Adriana Danowski, Roger A. Levy, Thomas L. Ortel, Anisur Rahman, Jane E. Salmon, … Michael D. Lockshin  
*Autoimmunity Reviews* (2014-06) <https://doi.org/ggp8r8>   
DOI: [10.1016/j.autrev.2014.01.053](https://doi.org/10.1016/j.autrev.2014.01.053) · PMID: [24468415](https://www.ncbi.nlm.nih.gov/pubmed/24468415)

101. **What is the role of hydroxychloroquine in reducing thrombotic risk in patients with antiphospholipid antibodies?**   
Tzu-Fei Wang, Wendy Lim  
*Hematology* (2016-12-02) <https://doi.org/ggrn3k>   
DOI: [10.1182/asheducation-2016.1.714](https://doi.org/10.1182/asheducation-2016.1.714) · PMID: [27913551](https://www.ncbi.nlm.nih.gov/pubmed/27913551) · PMCID: [PMC6142483](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6142483)

102. **COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression**   
Dan Zhou, Sheng-Ming Dai, Qiang Tong  
*Journal of Antimicrobial Chemotherapy* (2020-07) <https://doi.org/ggq84c>   
DOI: [10.1093/jac/dkaa114](https://doi.org/10.1093/jac/dkaa114) · PMID: [32196083](https://www.ncbi.nlm.nih.gov/pubmed/32196083) · PMCID: [PMC7184499](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7184499)

103. **Hydroxychloroquine treatment of patients with human immunodeficiency virus type 1**   
Kirk Sperber, Michael Louie, Thomas Kraus, Jacqueline Proner, Erica Sapira, Su Lin, Vera Stecher, Lloyd Mayer  
*Clinical Therapeutics* (1995-07) <https://doi.org/cq2hx9>   
DOI: [10.1016/0149-2918(95)80039-5](https://doi.org/10.1016/0149-2918(95)80039-5)

104. **Hydroxychloroquine augments early virological response to pegylated interferon plus ribavirin in genotype-4 chronic hepatitis C patients**   
Gouda Kamel Helal, Magdy Abdelmawgoud Gad, Mohamed Fahmy Abd-Ellah, Mahmoud Saied Eid  
*Journal of Medical Virology* (2016-12) <https://doi.org/f889nt>   
DOI: [10.1002/jmv.24575](https://doi.org/10.1002/jmv.24575) · PMID: [27183377](https://www.ncbi.nlm.nih.gov/pubmed/27183377) · PMCID: [PMC7167065](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7167065)

105. **Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial**   
Philippe Gautret, Jean-Christophe Lagier, Philippe Parola, Van Thuan Hoang, Line Meddeb, Morgane Mailhe, Barbara Doudier, Johan Courjon, Valérie Giordanengo, Vera Esteves Vieira, … Didier Raoult  
*International Journal of Antimicrobial Agents* (2020-07) <https://doi.org/dp7d>   
DOI: [10.1016/j.ijantimicag.2020.105949](https://doi.org/10.1016/j.ijantimicag.2020.105949) · PMID: [32205204](https://www.ncbi.nlm.nih.gov/pubmed/32205204) · PMCID: [PMC7102549](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102549)

106. **Official Statement from International Society of Antimicrobial Chemotherapy**   
Andreas Voss  
(2020-04-03) <https://www.isac.world/news-and-publications/official-isac-statement>

107. **No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection**   
J. M. Molina, C. Delaugerre, J. Le Goff, B. Mela-Lima, D. Ponscarme, L. Goldwirt, N. de Castro  
*Médecine et Maladies Infectieuses* (2020-06) <https://doi.org/ggqzrb>   
DOI: [10.1016/j.medmal.2020.03.006](https://doi.org/10.1016/j.medmal.2020.03.006) · PMID: [32240719](https://www.ncbi.nlm.nih.gov/pubmed/32240719)

108. **Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial**   
Zhaowei Chen, Jijia Hu, Zongwei Zhang, Shan Jiang, Shoumeng Han, Dandan Yan, Ruhong Zhuang, Ben Hu, Zhan Zhang  
*Cold Spring Harbor Laboratory* (2020-04-10) <https://doi.org/ggqm4v>   
DOI: [10.1101/2020.03.22.20040758](https://doi.org/10.1101/2020.03.22.20040758)

109. **The Extent and Consequences of P-Hacking in Science**   
Megan L. Head, Luke Holman, Rob Lanfear, Andrew T. Kahn, Michael D. Jennions  
*PLOS Biology* (2015-03-13) <https://doi.org/4z7>   
DOI: [10.1371/journal.pbio.1002106](https://doi.org/10.1371/journal.pbio.1002106) · PMID: [25768323](https://www.ncbi.nlm.nih.gov/pubmed/25768323) · PMCID: [PMC4359000](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4359000)

110. **A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19)**   
CHEN Jun, LIU Danping, LIU Li, LIU Ping, XU Qingnian, XIA Lu, LING Yun, HUANG Dan, SONG Shuli, ZHANG Dandan, … LU Hongzhou  
*Journal of Zhejiang University (Medical Sciences)* (2020-03) <https://doi.org/10.3785/j.issn.1008-9292.2020.03.03>   
DOI: [10.3785/j.issn.1008-9292.2020.03.03](https://doi.org/10.3785/j.issn.1008-9292.2020.03.03)

111. **Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies**   
Jianjun Gao, Zhenxue Tian, Xu Yang  
*BioScience Trends* (2020-02-29) <https://doi.org/ggm3mv>   
DOI: [10.5582/bst.2020.01047](https://doi.org/10.5582/bst.2020.01047) · PMID: [32074550](https://www.ncbi.nlm.nih.gov/pubmed/32074550)

112. **Targeting the Endocytic Pathway and Autophagy Process as a Novel Therapeutic Strategy in COVID-19**   
Naidi Yang, Han-Ming Shen  
*International Journal of Biological Sciences* (2020) <https://doi.org/ggqspm>   
DOI: [10.7150/ijbs.45498](https://doi.org/10.7150/ijbs.45498) · PMID: [32226290](https://www.ncbi.nlm.nih.gov/pubmed/32226290) · PMCID: [PMC7098027](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7098027)

113. **SARS-CoV-2: an Emerging Coronavirus that Causes a Global Threat**   
Jun Zheng  
*International Journal of Biological Sciences* (2020) <https://doi.org/ggqspr>   
DOI: [10.7150/ijbs.45053](https://doi.org/10.7150/ijbs.45053) · PMID: [32226285](https://www.ncbi.nlm.nih.gov/pubmed/32226285) · PMCID: [PMC7098030](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7098030)

114. **RETRACTED: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis**   
Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel  
*The Lancet* (2020-05) <https://doi.org/ggwzsb>   
DOI: [10.1016/s0140-6736(20)31180-6](https://doi.org/10.1016/s0140-6736(20)31180-6) · PMID: [32450107](https://www.ncbi.nlm.nih.gov/pubmed/32450107) · PMCID: [PMC7255293](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7255293)

115. **Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis**   
Mandeep R Mehra, Frank Ruschitzka, Amit N Patel  
*The Lancet* (2020-06) <https://doi.org/ggzqng>   
DOI: [10.1016/s0140-6736(20)31324-6](https://doi.org/10.1016/s0140-6736(20)31324-6) · PMID: [32511943](https://www.ncbi.nlm.nih.gov/pubmed/32511943) · PMCID: [PMC7274621](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7274621)

116. **Life Threatening Severe QTc Prolongation in Patient with Systemic Lupus Erythematosus due to Hydroxychloroquine**   
John P. O’Laughlin, Parag H. Mehta, Brian C. Wong  
*Case Reports in Cardiology* (2016) <https://doi.org/ggqzrc>   
DOI: [10.1155/2016/4626279](https://doi.org/10.1155/2016/4626279) · PMID: [27478650](https://www.ncbi.nlm.nih.gov/pubmed/27478650) · PMCID: [PMC4960328](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4960328)

117. **Keep the QT interval: It is a reliable predictor of ventricular arrhythmias**   
Dan M. Roden  
*Heart Rhythm* (2008-08) <https://doi.org/d5rchx>   
DOI: [10.1016/j.hrthm.2008.05.008](https://doi.org/10.1016/j.hrthm.2008.05.008) · PMID: [18675237](https://www.ncbi.nlm.nih.gov/pubmed/18675237) · PMCID: [PMC3212752](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3212752)

118. **Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study**   
Jennifer C.E.Lane, James Weaver, Kristin Kostka, Talita Duarte-Salles, Maria Tereza F. Abrahao, Heba Alghoul, Osaid Alser, Thamir M Alshammari, Patricia Biedermann, Edward Burn, … Daniel Prieto-Alhambra  
*Cold Spring Harbor Laboratory* (2020-04-10) <https://doi.org/ggrn7s>   
DOI: [10.1101/2020.04.08.20054551](https://doi.org/10.1101/2020.04.08.20054551)

119. **Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial ( *CloroCovid-19 Study* )**   
Mayla Gabriela Silva Borba, Fernando Fonseca Almeida Val, Vanderson Souza Sampaio, Marcia Almeida Araújo Alexandre, Gisely Cardoso Melo, Marcelo Brito, Maria Paula Gomes Mourão, José Diego Brito-Sousa, Djane Baía-da-Silva, Marcus Vinitius Farias Guerra, … CloroCovid-19 Team  
*Cold Spring Harbor Laboratory* (2020-04-16) <https://doi.org/ggr3nj>   
DOI: [10.1101/2020.04.07.20056424](https://doi.org/10.1101/2020.04.07.20056424)

120. **Heart risk concerns mount around use of chloroquine and hydroxychloroquine for Covid-19 treatment**   
Jacqueline Howard, Elizabeth Cohen, Nadia Kounang, Per Nyberg  
*CNN* (2020-04-14) <https://www.cnn.com/2020/04/13/health/chloroquine-risks-coronavirus-treatment-trials-study/index.html>

121. **WHO Director-General’s opening remarks at the media briefing on COVID-19**   
World Health Organization  
(2020-05-25) <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---25-may-2020>

122. **Hydroxychloroquine in patients mainly with mild to moderate COVID–19: an open–label, randomized, controlled trial**   
Wei Tang, Zhujun Cao, Mingfeng Han, Zhengyan Wang, Junwen Chen, Wenjin Sun, Yaojie Wu, Wei Xiao, Shengyong Liu, Erzhen Chen, … Qing Xie  
*Cold Spring Harbor Laboratory* (2020-05-07) <https://doi.org/ggr68m>   
DOI: [10.1101/2020.04.10.20060558](https://doi.org/10.1101/2020.04.10.20060558)

123. **Detection of SARS-CoV-2 in Different Types of Clinical Specimens**   
Wenling Wang, Yanli Xu, Ruqin Gao, Roujian Lu, Kai Han, Guizhen Wu, Wenjie Tan  
*JAMA* (2020-03-11) <https://doi.org/ggpp6h>   
DOI: [10.1001/jama.2020.3786](https://doi.org/10.1001/jama.2020.3786) · PMID: [32159775](https://www.ncbi.nlm.nih.gov/pubmed/32159775) · PMCID: [PMC7066521](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7066521)

124. **Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19**   
Joseph Magagnoli, Siddharth Narendran, Felipe Pereira, Tammy Cummings, James W. Hardin, S. Scott Sutton, Jayakrishna Ambati  
*Cold Spring Harbor Laboratory* (2020-04-21) <https://doi.org/ggspt6>   
DOI: [10.1101/2020.04.16.20065920](https://doi.org/10.1101/2020.04.16.20065920) · PMID: [32511622](https://www.ncbi.nlm.nih.gov/pubmed/32511622) · PMCID: [PMC7276049](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7276049)

125. **Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19**   
The RECOVERY Collaborative Group  
*New England Journal of Medicine* (2020-11-19) <https://doi.org/ghd8c7>   
DOI: [10.1056/nejmoa2022926](https://doi.org/10.1056/nejmoa2022926) · PMID: [33031652](https://www.ncbi.nlm.nih.gov/pubmed/33031652) · PMCID: [PMC7556338](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7556338)

126. **Hydroxychloroquine for Early Treatment of Adults With Mild Coronavirus Disease 2019: A Randomized, Controlled Trial**   
Oriol Mitjà, Marc Corbacho-Monné, Maria Ubals, Cristian Tebé, Judith Peñafiel, Aurelio Tobias, Ester Ballana, Andrea Alemany, Núria Riera-Martí, Carla A Pérez, … Martí Vall-Mayans  
*Clinical Infectious Diseases* (2020-07-16) <https://doi.org/gg5f9x>   
DOI: [10.1093/cid/ciaa1009](https://doi.org/10.1093/cid/ciaa1009) · PMID: [32674126](https://www.ncbi.nlm.nih.gov/pubmed/32674126) · PMCID: [PMC7454406](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7454406)

127. **A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19**   
David R. Boulware, Matthew F. Pullen, Ananta S. Bangdiwala, Katelyn A. Pastick, Sarah M. Lofgren, Elizabeth C. Okafor, Caleb P. Skipper, Alanna A. Nascene, Melanie R. Nicol, Mahsa Abassi, … Kathy H. Hullsiek  
*New England Journal of Medicine* (2020-08-06) <https://doi.org/dxkv>   
DOI: [10.1056/nejmoa2016638](https://doi.org/10.1056/nejmoa2016638) · PMID: [32492293](https://www.ncbi.nlm.nih.gov/pubmed/32492293) · PMCID: [PMC7289276](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7289276)

128. **Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure SARS-CoV-2 Prophylaxis Among Health Care Workers**   
Benjamin S. Abella, Eliana L. Jolkovsky, Barbara T. Biney, Julie E. Uspal, Matthew C. Hyman, Ian Frank, Scott E. Hensley, Saar Gill, Dan T. Vogl, Ivan Maillard, … Prevention and Treatment of COVID-19 With Hydroxychloroquine (PATCH) Investigators  
*JAMA Internal Medicine* (2021-02-01) <https://doi.org/ghd6nj>   
DOI: [10.1001/jamainternmed.2020.6319](https://doi.org/10.1001/jamainternmed.2020.6319) · PMID: [33001138](https://www.ncbi.nlm.nih.gov/pubmed/33001138) · PMCID: [PMC7527945](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7527945)

129. **Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology**   
Eva Schrezenmeier, Thomas Dörner  
*Nature Reviews Rheumatology* (2020-02-07) <https://doi.org/ggzjnh>   
DOI: [10.1038/s41584-020-0372-x](https://doi.org/10.1038/s41584-020-0372-x) · PMID: [32034323](https://www.ncbi.nlm.nih.gov/pubmed/32034323)

130. **Synthesis and Pharmacology of Anti-Inflammatory Steroidal Antedrugs**   
M. Omar F. Khan, Henry J. Lee  
*Chemical Reviews* (2008-12-10) <https://doi.org/cmkrtc>   
DOI: [10.1021/cr068203e](https://doi.org/10.1021/cr068203e) · PMID: [19035773](https://www.ncbi.nlm.nih.gov/pubmed/19035773) · PMCID: [PMC2650492](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2650492)

131. **Drug vignettes: Dexamethasone**   
The Centre for Evidence-Based Medicine  
<https://www.cebm.net/covid-19/dexamethasone/>

132. **16-METHYLATED STEROIDS. I. 16α-METHYLATED ANALOGS OF CORTISONE, A NEW GROUP OF ANTI-INFLAMMATORY STEROIDS**   
Glen E. Arth, David B. R. Johnston, John Fried, William W. Spooncer, Dale R. Hoff, Lewis H. Sarett  
*Journal of the American Chemical Society* (2002-05-01) <https://doi.org/cj5c82>   
DOI: [10.1021/ja01545a061](https://doi.org/10.1021/ja01545a061)

133. **Treatment of Rheumatoid Arthritis with Dexamethasone**   
Abraham Cohen  
*JAMA* (1960-10-15) <https://doi.org/csfmhc>   
DOI: [10.1001/jama.1960.03030070009002](https://doi.org/10.1001/jama.1960.03030070009002) · PMID: [13694317](https://www.ncbi.nlm.nih.gov/pubmed/13694317)

134. **Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia**   
Wei Zhou, Yisi Liu, Dongdong Tian, Cheng Wang, Sa Wang, Jing Cheng, Ming Hu, Minghao Fang, Yue Gao  
*Signal Transduction and Targeted Therapy* (2020-02-21) <https://doi.org/ggqr84>   
DOI: [10.1038/s41392-020-0127-9](https://doi.org/10.1038/s41392-020-0127-9) · PMID: [32296012](https://www.ncbi.nlm.nih.gov/pubmed/32296012) · PMCID: [PMC7035340](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7035340)

135. **Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial**   
Jesús Villar, Carlos Ferrando, Domingo Martínez, Alfonso Ambrós, Tomás Muñoz, Juan A Soler, Gerardo Aguilar, Francisco Alba, Elena González-Higueras, Luís A Conesa, … Jesús Villar  
*The Lancet Respiratory Medicine* (2020-03) <https://doi.org/ggpxzc>   
DOI: [10.1016/s2213-2600(19)30417-5](https://doi.org/10.1016/s2213-2600(19)30417-5)

136. **Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury**   
Clark D Russell, Jonathan E Millar, J Kenneth Baillie  
*The Lancet* (2020-02) <https://doi.org/ggks86>   
DOI: [10.1016/s0140-6736(20)30317-2](https://doi.org/10.1016/s0140-6736(20)30317-2) · PMID: [32043983](https://www.ncbi.nlm.nih.gov/pubmed/32043983) · PMCID: [PMC7134694](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7134694)

137. **On the use of corticosteroids for 2019-nCoV pneumonia**   
Lianhan Shang, Jianping Zhao, Yi Hu, Ronghui Du, Bin Cao  
*The Lancet* (2020-02) <https://doi.org/ggq356>   
DOI: [10.1016/s0140-6736(20)30361-5](https://doi.org/10.1016/s0140-6736(20)30361-5) · PMID: [32122468](https://www.ncbi.nlm.nih.gov/pubmed/32122468) · PMCID: [PMC7159292](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7159292)

138. **Pharmacology of Postoperative Nausea and Vomiting**   
Eric S. Zabirowicz, Tong J. Gan  
*Elsevier BV* (2019) <https://doi.org/ghfkjw>   
DOI: [10.1016/b978-0-323-48110-6.00034-x](https://doi.org/10.1016/b978-0-323-48110-6.00034-x)

139. **Non-traditional cytokines: How catecholamines and adipokines influence macrophages in immunity, metabolism and the central nervous system**   
Mark A. Barnes, Monica J. Carson, Meera G. Nair  
*Cytokine* (2015-04) <https://doi.org/f65c59>   
DOI: [10.1016/j.cyto.2015.01.008](https://doi.org/10.1016/j.cyto.2015.01.008) · PMID: [25703786](https://www.ncbi.nlm.nih.gov/pubmed/25703786) · PMCID: [PMC4590987](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4590987)

140. **Stress Hormones, Proinflammatory and Antiinflammatory Cytokines, and Autoimmunity**   
ILIA J. ELENKOV, GEORGE P. CHROUSOS  
*Annals of the New York Academy of Sciences* (2002-06) <https://doi.org/fmwpx2>   
DOI: [10.1111/j.1749-6632.2002.tb04229.x](https://doi.org/10.1111/j.1749-6632.2002.tb04229.x) · PMID: [12114286](https://www.ncbi.nlm.nih.gov/pubmed/12114286)

141. **Recovery of the Hypothalamic-Pituitary-Adrenal Response to Stress**   
Arantxa García, Octavi Martí, Astrid Vallès, Silvina Dal-Zotto, Antonio Armario  
*Neuroendocrinology* (2000) <https://doi.org/b2cq8n>   
DOI: [10.1159/000054578](https://doi.org/10.1159/000054578) · PMID: [10971146](https://www.ncbi.nlm.nih.gov/pubmed/10971146)

142. **Modulatory effects of glucocorticoids and catecholamines on human interleukin-12 and interleukin-10 production: clinical implications.**   
IJ Elenkov, DA Papanicolaou, RL Wilder, GP Chrousos  
*Proceedings of the Association of American Physicians* (1996-09) <https://www.ncbi.nlm.nih.gov/pubmed/8902882>   
PMID: [8902882](https://www.ncbi.nlm.nih.gov/pubmed/8902882)

143. **Prevention of infection caused by immunosuppressive drugs in gastroenterology**   
Katarzyna Orlicka, Eleanor Barnes, Emma L. Culver  
*Therapeutic Advances in Chronic Disease* (2013-04-22) <https://doi.org/ggrqd3>   
DOI: [10.1177/2040622313485275](https://doi.org/10.1177/2040622313485275) · PMID: [23819020](https://www.ncbi.nlm.nih.gov/pubmed/23819020) · PMCID: [PMC3697844](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3697844)

144. **COVID-19: consider cytokine storm syndromes and immunosuppression**   
Puja Mehta, Daniel F McAuley, Michael Brown, Emilie Sanchez, Rachel S Tattersall, Jessica J Manson  
*The Lancet* (2020-03) <https://doi.org/ggnzmc>   
DOI: [10.1016/s0140-6736(20)30628-0](https://doi.org/10.1016/s0140-6736(20)30628-0)

145. **Immunosuppression for hyperinflammation in COVID-19: a double-edged sword?**   
Andrew I Ritchie, Aran Singanayagam  
*The Lancet* (2020-04) <https://doi.org/ggq8hs>   
DOI: [10.1016/s0140-6736(20)30691-7](https://doi.org/10.1016/s0140-6736(20)30691-7) · PMID: [32220278](https://www.ncbi.nlm.nih.gov/pubmed/32220278) · PMCID: [PMC7138169](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7138169)

146. **Effect of Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report**   
Peter Horby, Wei Shen Lim, Jonathan Emberson, Marion Mafham, Jennifer Bell, Louise Linsell, Natalie Staplin, Christopher Brightling, Andrew Ustianowski, Einas Elmahi, … RECOVERY Collaborative Group  
*Cold Spring Harbor Laboratory* (2020-06-22) <https://doi.org/dz5x>   
DOI: [10.1101/2020.06.22.20137273](https://doi.org/10.1101/2020.06.22.20137273)

147. **Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report**   
The RECOVERY Collaborative Group  
*New England Journal of Medicine* (2020-07-17) <https://doi.org/gg5c8p>   
DOI: [10.1056/nejmoa2021436](https://doi.org/10.1056/nejmoa2021436) · PMID: [32678530](https://www.ncbi.nlm.nih.gov/pubmed/32678530) · PMCID: [PMC7383595](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7383595)

148. **Corticosteroids for Patients With Coronavirus Disease 2019 (COVID-19) With Different Disease Severity: A Meta-Analysis of Randomized Clinical Trials**   
Laura Pasin, Paolo Navalesi, Alberto Zangrillo, Artem Kuzovlev, Valery Likhvantsev, Ludhmila Abrahão Hajjar, Stefano Fresilli, Marcus Vinicius Guimaraes Lacerda, Giovanni Landoni  
*Journal of Cardiothoracic and Vascular Anesthesia* (2021-02) <https://doi.org/ghzkp9>   
DOI: [10.1053/j.jvca.2020.11.057](https://doi.org/10.1053/j.jvca.2020.11.057) · PMID: [33298370](https://www.ncbi.nlm.nih.gov/pubmed/33298370) · PMCID: [PMC7698829](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7698829)

149. **Current concepts in the diagnosis and management of cytokine release syndrome**   
Daniel W. Lee, Rebecca Gardner, David L. Porter, Chrystal U. Louis, Nabil Ahmed, Michael Jensen, Stephan A. Grupp, Crystal L. Mackall  
*Blood* (2014-07-10) <https://doi.org/ggsrwk>   
DOI: [10.1182/blood-2014-05-552729](https://doi.org/10.1182/blood-2014-05-552729) · PMID: [24876563](https://www.ncbi.nlm.nih.gov/pubmed/24876563) · PMCID: [PMC4093680](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4093680)

150. **Dexamethasone for COVID-19? Not so fast.**   
T. C. Theoharides  
*JOURNAL OF BIOLOGICAL REGULATORS AND HOMEOSTATIC AGENTS* (2020-08-31) <https://doi.org/ghfkjx>   
DOI: [10.23812/20-editorial\_1-5](https://doi.org/10.23812/20-editorial_1-5) · PMID: [32551464](https://www.ncbi.nlm.nih.gov/pubmed/32551464)

151. **Dexamethasone in hospitalised patients with COVID-19: addressing uncertainties**   
Michael A Matthay, B Taylor Thompson  
*The Lancet Respiratory Medicine* (2020-12) <https://doi.org/ftk4>   
DOI: [10.1016/s2213-2600(20)30503-8](https://doi.org/10.1016/s2213-2600(20)30503-8) · PMID: [33129421](https://www.ncbi.nlm.nih.gov/pubmed/33129421) · PMCID: [PMC7598750](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7598750)

152. **Dexamethasone for COVID-19: data needed from randomised clinical trials in Africa**   
Helen Brotherton, Effua Usuf, Behzad Nadjm, Karen Forrest, Kalifa Bojang, Ahmadou Lamin Samateh, Mustapha Bittaye, Charles AP Roberts, Umberto d’Alessandro, Anna Roca  
*The Lancet Global Health* (2020-09) <https://doi.org/gg42kx>   
DOI: [10.1016/s2214-109x(20)30318-1](https://doi.org/10.1016/s2214-109x(20)30318-1) · PMID: [32679038](https://www.ncbi.nlm.nih.gov/pubmed/32679038) · PMCID: [PMC7833918](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7833918)

153. **Formulation and manufacturability of biologics**   
Steven J Shire  
*Current Opinion in Biotechnology* (2009-12) <https://doi.org/cjk8p6>   
DOI: [10.1016/j.copbio.2009.10.006](https://doi.org/10.1016/j.copbio.2009.10.006) · PMID: [19880308](https://www.ncbi.nlm.nih.gov/pubmed/19880308)

154. **Early Development of Therapeutic Biologics - Pharmacokinetics**   
A. Baumann  
*Current Drug Metabolism* (2006-01-01) <https://doi.org/bhcz79>   
DOI: [10.2174/138920006774832604](https://doi.org/10.2174/138920006774832604) · PMID: [16454690](https://www.ncbi.nlm.nih.gov/pubmed/16454690)

155. **Deriving Immune Modulating Drugs from Viruses—A New Class of Biologics**   
Jordan R. Yaron, Liqiang Zhang, Qiuyun Guo, Michelle Burgin, Lauren N. Schutz, Enkidia Awo, Lyn Wise, Kurt L. Krause, Cristhian J. Ildefonso, Jacek M. Kwiecien, … Alexandra R. Lucas  
*Journal of Clinical Medicine* (2020-03-31) <https://doi.org/ghdx73>   
DOI: [10.3390/jcm9040972](https://doi.org/10.3390/jcm9040972) · PMID: [32244484](https://www.ncbi.nlm.nih.gov/pubmed/32244484) · PMCID: [PMC7230489](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7230489)

156. **IL-6 in Inflammation, Immunity, and Disease**   
T. Tanaka, M. Narazaki, T. Kishimoto  
*Cold Spring Harbor Perspectives in Biology* (2014-09-04) <https://doi.org/gftpjs>   
DOI: [10.1101/cshperspect.a016295](https://doi.org/10.1101/cshperspect.a016295) · PMID: [25190079](https://www.ncbi.nlm.nih.gov/pubmed/25190079) · PMCID: [PMC4176007](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4176007)

157. **Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study**   
Fei Zhou, Ting Yu, Ronghui Du, Guohui Fan, Ying Liu, Zhibo Liu, Jie Xiang, Yeming Wang, Bin Song, Xiaoying Gu, … Bin Cao  
*The Lancet* (2020-03) <https://doi.org/ggnxb3>   
DOI: [10.1016/s0140-6736(20)30566-3](https://doi.org/10.1016/s0140-6736(20)30566-3)

158. **Into the Eye of the Cytokine Storm**   
J. R. Tisoncik, M. J. Korth, C. P. Simmons, J. Farrar, T. R. Martin, M. G. Katze  
*Microbiology and Molecular Biology Reviews* (2012-03-05) <https://doi.org/f4n9h2>   
DOI: [10.1128/mmbr.05015-11](https://doi.org/10.1128/mmbr.05015-11) · PMID: [22390970](https://www.ncbi.nlm.nih.gov/pubmed/22390970) · PMCID: [PMC3294426](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294426)

159. **Hall of Fame among Pro-inflammatory Cytokines: Interleukin-6 Gene and Its Transcriptional Regulation Mechanisms**   
Yang Luo, Song Guo Zheng  
*Frontiers in Immunology* (2016-12-19) <https://doi.org/ggqmgv>   
DOI: [10.3389/fimmu.2016.00604](https://doi.org/10.3389/fimmu.2016.00604) · PMID: [28066415](https://www.ncbi.nlm.nih.gov/pubmed/28066415) · PMCID: [PMC5165036](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5165036)

160. **IL-6 Trans-Signaling via the Soluble IL-6 Receptor: Importance for the Pro-Inflammatory Activities of IL-6**   
Stefan Rose-John  
*International Journal of Biological Sciences* (2012) <https://doi.org/f4c4hf>   
DOI: [10.7150/ijbs.4989](https://doi.org/10.7150/ijbs.4989) · PMID: [23136552](https://www.ncbi.nlm.nih.gov/pubmed/23136552) · PMCID: [PMC3491447](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3491447)

161. **Interleukin-6 and its receptor: from bench to bedside**   
Jürgen Scheller, Stefan Rose-John  
*Medical Microbiology and Immunology* (2006-05-31) <https://doi.org/ck8xch>   
DOI: [10.1007/s00430-006-0019-9](https://doi.org/10.1007/s00430-006-0019-9) · PMID: [16741736](https://www.ncbi.nlm.nih.gov/pubmed/16741736)

162. **Plasticity and cross-talk of Interleukin 6-type cytokines**   
Christoph Garbers, Heike M. Hermanns, Fred Schaper, Gerhard Müller-Newen, Joachim Grötzinger, Stefan Rose-John, Jürgen Scheller  
*Cytokine & Growth Factor Reviews* (2012-06) <https://doi.org/f3z743>   
DOI: [10.1016/j.cytogfr.2012.04.001](https://doi.org/10.1016/j.cytogfr.2012.04.001) · PMID: [22595692](https://www.ncbi.nlm.nih.gov/pubmed/22595692)

163. **Soluble receptors for cytokines and growth factors: generation and biological function**   
S Rose-John, PC Heinrich  
*Biochemical Journal* (1994-06-01) <https://doi.org/ggqmgd>   
DOI: [10.1042/bj3000281](https://doi.org/10.1042/bj3000281) · PMID: [8002928](https://www.ncbi.nlm.nih.gov/pubmed/8002928) · PMCID: [PMC1138158](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1138158)

164. **Interleukin-6; pathogenesis and treatment of autoimmune inflammatory diseases**   
Toshio Tanaka, Masashi Narazaki, Kazuya Masuda, Tadamitsu Kishimoto  
*Inflammation and Regeneration* (2013) <https://doi.org/ggqmgt>   
DOI: [10.2492/inflammregen.33.054](https://doi.org/10.2492/inflammregen.33.054)

165. **Effective treatment of severe COVID-19 patients with tocilizumab**   
Xiaoling Xu, Mingfeng Han, Tiantian Li, Wei Sun, Dongsheng Wang, Binqing Fu, Yonggang Zhou, Xiaohu Zheng, Yun Yang, Xiuyong Li, … Haiming Wei  
*Proceedings of the National Academy of Sciences* (2020-05-19) <https://doi.org/ggv3r3>   
DOI: [10.1073/pnas.2005615117](https://doi.org/10.1073/pnas.2005615117) · PMID: [32350134](https://www.ncbi.nlm.nih.gov/pubmed/32350134) · PMCID: [PMC7245089](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7245089)

166. **Tocilizumab in patients with severe COVID-19: a retrospective cohort study**   
Giovanni Guaraldi, Marianna Meschiari, Alessandro Cozzi-Lepri, Jovana Milic, Roberto Tonelli, Marianna Menozzi, Erica Franceschini, Gianluca Cuomo, Gabriella Orlando, Vanni Borghi, … Cristina Mussini  
*The Lancet Rheumatology* (2020-08) <https://doi.org/d2pk>   
DOI: [10.1016/s2665-9913(20)30173-9](https://doi.org/10.1016/s2665-9913(20)30173-9) · PMID: [32835257](https://www.ncbi.nlm.nih.gov/pubmed/32835257) · PMCID: [PMC7314456](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7314456)

167. **Tocilizumab Treatment for Cytokine Release Syndrome in Hospitalized Patients With Coronavirus Disease 2019**   
Christina C. Price, Frederick L. Altice, Yu Shyr, Alan Koff, Lauren Pischel, George Goshua, Marwan M. Azar, Dayna Mcmanus, Sheau-Chiann Chen, Shana E. Gleeson, … Maricar Malinis  
*Chest* (2020-10) <https://doi.org/gg2789>   
DOI: [10.1016/j.chest.2020.06.006](https://doi.org/10.1016/j.chest.2020.06.006) · PMID: [32553536](https://www.ncbi.nlm.nih.gov/pubmed/32553536) · PMCID: [PMC7831876](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7831876)

168. **Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia**   
Ruggero Capra, Nicola De Rossi, Flavia Mattioli, Giuseppe Romanelli, Cristina Scarpazza, Maria Pia Sormani, Stefania Cossi  
*European Journal of Internal Medicine* (2020-06) <https://doi.org/ggx4fm>   
DOI: [10.1016/j.ejim.2020.05.009](https://doi.org/10.1016/j.ejim.2020.05.009) · PMID: [32405160](https://www.ncbi.nlm.nih.gov/pubmed/32405160) · PMCID: [PMC7219361](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7219361)

169. **Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients**   
T. Klopfenstein, S. Zayet, A. Lohse, J.-C. Balblanc, J. Badie, P.-Y. Royer, L. Toko, C. Mezher, N. J. Kadiane-Oussou, M. Bossert, … T. Conrozier  
*Médecine et Maladies Infectieuses* (2020-08) <https://doi.org/ggvz45>   
DOI: [10.1016/j.medmal.2020.05.001](https://doi.org/10.1016/j.medmal.2020.05.001) · PMID: [32387320](https://www.ncbi.nlm.nih.gov/pubmed/32387320) · PMCID: [PMC7202806](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7202806)

170. **Outcomes in patients with severe COVID-19 disease treated with tocilizumab: a case–controlled study**   
G Rojas-Marte, M Khalid, O Mukhtar, AT Hashmi, MA Waheed, S Ehrlich, A Aslam, S Siddiqui, C Agarwal, Y Malyshev, … J Shani  
*QJM: An International Journal of Medicine* (2020-08) <https://doi.org/gg496t>   
DOI: [10.1093/qjmed/hcaa206](https://doi.org/10.1093/qjmed/hcaa206) · PMID: [32569363](https://www.ncbi.nlm.nih.gov/pubmed/32569363) · PMCID: [PMC7337835](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7337835)

171. **Systematic Review and Meta-Analysis of Case-Control Studies from 7,000 COVID-19 Pneumonia Patients Suggests a Beneficial Impact of Tocilizumab with Benefit Most Evident in Non-Corticosteroid Exposed Subjects.**   
Abdulla Watad, Nicola Luigi Bragazzi, Charlie Bridgewood, Muhammad Mansour, Naim Mahroum, Matteo Riccò, Ahmed Nasr, Amr Hussein, Omer Gendelman, Yehuda Shoenfeld, … Dennis McGonagle  
*SSRN Electronic Journal* (2020) <https://doi.org/gg62hz>   
DOI: [10.2139/ssrn.3642653](https://doi.org/10.2139/ssrn.3642653)

172. **The efficacy of IL-6 inhibitor Tocilizumab in reducing severe COVID-19 mortality: a systematic review**   
Avi Gurion Kaye, Robert Siegel  
*PeerJ* (2020-11-02) <https://doi.org/ghx8r4>   
DOI: [10.7717/peerj.10322](https://doi.org/10.7717/peerj.10322) · PMID: [33194450](https://www.ncbi.nlm.nih.gov/pubmed/33194450) · PMCID: [PMC7643559](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7643559)

173. **Rationale and evidence on the use of tocilizumab in COVID-19: a systematic review**   
A. Cortegiani, M. Ippolito, M. Greco, V. Granone, A. Protti, C. Gregoretti, A. Giarratano, S. Einav, M. Cecconi  
*Pulmonology* (2021-01) <https://doi.org/gg5xv3>   
DOI: [10.1016/j.pulmoe.2020.07.003](https://doi.org/10.1016/j.pulmoe.2020.07.003) · PMID: [32713784](https://www.ncbi.nlm.nih.gov/pubmed/32713784) · PMCID: [PMC7369580](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7369580)

174. **New insights and long-term safety of tocilizumab in rheumatoid arthritis**   
Graeme Jones, Elena Panova  
*Therapeutic Advances in Musculoskeletal Disease* (2018-10-07) <https://doi.org/gffsdt>   
DOI: [10.1177/1759720x18798462](https://doi.org/10.1177/1759720x18798462) · PMID: [30327685](https://www.ncbi.nlm.nih.gov/pubmed/30327685) · PMCID: [PMC6178374](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6178374)

175. **Tocilizumab during pregnancy and lactation: drug levels in maternal serum, cord blood, breast milk and infant serum**   
Jumpei Saito, Naho Yakuwa, Kayoko Kaneko, Chinatsu Takai, Mikako Goto, Ken Nakajima, Akimasa Yamatani, Atsuko Murashima  
*Rheumatology* (2019-08) <https://doi.org/ggzhks>   
DOI: [10.1093/rheumatology/kez100](https://doi.org/10.1093/rheumatology/kez100) · PMID: [30945743](https://www.ncbi.nlm.nih.gov/pubmed/30945743)

176. **Short-course tocilizumab increases risk of hepatitis B virus reactivation in patients with rheumatoid arthritis: a prospective clinical observation**   
Le-Feng Chen, Ying-Qian Mo, Jun Jing, Jian-Da Ma, Dong-Hui Zheng, Lie Dai  
*International Journal of Rheumatic Diseases* (2017-07) <https://doi.org/f9pbc5>   
DOI: [10.1111/1756-185x.13010](https://doi.org/10.1111/1756-185x.13010) · PMID: [28160426](https://www.ncbi.nlm.nih.gov/pubmed/28160426)

177. **Why tocilizumab could be an effective treatment for severe COVID-19?**   
Binqing Fu, Xiaoling Xu, Haiming Wei  
*Journal of Translational Medicine* (2020-04-14) <https://doi.org/ggv5c8>   
DOI: [10.1186/s12967-020-02339-3](https://doi.org/10.1186/s12967-020-02339-3) · PMID: [32290839](https://www.ncbi.nlm.nih.gov/pubmed/32290839) · PMCID: [PMC7154566](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7154566)

178. **Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials**   
L. Campbell, C. Chen, S. S. Bhagat, R. A. Parker, A. J. K. Ostor  
*Rheumatology* (2010-11-14) <https://doi.org/crqn7c>   
DOI: [10.1093/rheumatology/keq343](https://doi.org/10.1093/rheumatology/keq343) · PMID: [21078627](https://www.ncbi.nlm.nih.gov/pubmed/21078627)

179. **Risk of serious infections in tocilizumab versus other biologic drugs in patients with rheumatoid arthritis: a multidatabase cohort study**   
Ajinkya Pawar, Rishi J Desai, Daniel H Solomon, Adrian J Santiago Ortiz, Sara Gale, Min Bao, Khaled Sarsour, Sebastian Schneeweiss, Seoyoung C Kim  
*Annals of the Rheumatic Diseases* (2019-04) <https://doi.org/gg62hx>   
DOI: [10.1136/annrheumdis-2018-214367](https://doi.org/10.1136/annrheumdis-2018-214367) · PMID: [30679153](https://www.ncbi.nlm.nih.gov/pubmed/30679153)

180. **Risk of infections in rheumatoid arthritis patients treated with tocilizumab**   
Veronika R. Lang, Matthias Englbrecht, Jürgen Rech, Hubert Nüsslein, Karin Manger, Florian Schuch, Hans-Peter Tony, Martin Fleck, Bernhard Manger, Georg Schett, Jochen Zwerina  
*Rheumatology* (2012-05) <https://doi.org/d3b3rh>   
DOI: [10.1093/rheumatology/ker223](https://doi.org/10.1093/rheumatology/ker223) · PMID: [21865281](https://www.ncbi.nlm.nih.gov/pubmed/21865281)

181. **Use of Tocilizumab for COVID-19-Induced Cytokine Release Syndrome**   
Jared Radbel, Navaneeth Narayanan, Pinki J. Bhatt  
*Chest* (2020-07) <https://doi.org/ggtxvs>   
DOI: [10.1016/j.chest.2020.04.024](https://doi.org/10.1016/j.chest.2020.04.024) · PMID: [32343968](https://www.ncbi.nlm.nih.gov/pubmed/32343968) · PMCID: [PMC7195070](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7195070)

182. **The Efficacy of IL-6 Inhibitor Tocilizumab in Reducing Severe COVID-19 Mortality: A Systematic Review**   
Avi Kaye, Robert Siegel  
*Cold Spring Harbor Laboratory* (2020-07-14) <https://doi.org/gg62hv>   
DOI: [10.1101/2020.07.10.20150938](https://doi.org/10.1101/2020.07.10.20150938)

183. **Utilizing tocilizumab for the treatment of cytokine release syndrome in COVID-19**   
Ali Hassoun, Elizabeth Dilip Thottacherry, Justin Muklewicz, Qurrat-ul-ain Aziz, Jonathan Edwards  
*Journal of Clinical Virology* (2020-07) <https://doi.org/ggx359>   
DOI: [10.1016/j.jcv.2020.104443](https://doi.org/10.1016/j.jcv.2020.104443) · PMID: [32425661](https://www.ncbi.nlm.nih.gov/pubmed/32425661) · PMCID: [PMC7229471](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7229471)

184. **Development of therapeutic antibodies for the treatment of diseases**   
Ruei-Min Lu, Yu-Chyi Hwang, I-Ju Liu, Chi-Chiu Lee, Han-Zen Tsai, Hsin-Jung Li, Han-Chung Wu  
*Journal of Biomedical Science* (2020-01-02) <https://doi.org/ggqbpx>   
DOI: [10.1186/s12929-019-0592-z](https://doi.org/10.1186/s12929-019-0592-z) · PMID: [31894001](https://www.ncbi.nlm.nih.gov/pubmed/31894001) · PMCID: [PMC6939334](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6939334)

185. **Broadly Neutralizing Antiviral Antibodies**   
Davide Corti, Antonio Lanzavecchia  
*Annual Review of Immunology* (2013-03-21) <https://doi.org/gf25g8>   
DOI: [10.1146/annurev-immunol-032712-095916](https://doi.org/10.1146/annurev-immunol-032712-095916) · PMID: [23330954](https://www.ncbi.nlm.nih.gov/pubmed/23330954)

186. **Ibalizumab Targeting CD4 Receptors, An Emerging Molecule in HIV Therapy**   
Simona A. Iacob, Diana G. Iacob  
*Frontiers in Microbiology* (2017-11-27) <https://doi.org/gcn3kh>   
DOI: [10.3389/fmicb.2017.02323](https://doi.org/10.3389/fmicb.2017.02323) · PMID: [29230203](https://www.ncbi.nlm.nih.gov/pubmed/29230203) · PMCID: [PMC5711820](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5711820)

187. **Product review on the monoclonal antibody palivizumab for prevention of respiratory syncytial virus infection**   
Bernhard Resch  
*Human Vaccines & Immunotherapeutics* (2017-06-12) <https://doi.org/ggqbps>   
DOI: [10.1080/21645515.2017.1337614](https://doi.org/10.1080/21645515.2017.1337614) · PMID: [28605249](https://www.ncbi.nlm.nih.gov/pubmed/28605249) · PMCID: [PMC5612471](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5612471)

188. **Chronological evolution of IgM, IgA, IgG and neutralisation antibodies after infection with SARS-associated coronavirus**   
P.-R. Hsueh, L.-M. Huang, P.-J. Chen, C.-L. Kao, P.-C. Yang  
*Clinical Microbiology and Infection* (2004-12) <https://doi.org/cwwg87>   
DOI: [10.1111/j.1469-0691.2004.01009.x](https://doi.org/10.1111/j.1469-0691.2004.01009.x) · PMID: [15606632](https://www.ncbi.nlm.nih.gov/pubmed/15606632)

189. **Neutralizing Antibodies in Patients with Severe Acute Respiratory Syndrome-Associated Coronavirus Infection**   
Nie Yuchun, Wang Guangwen, Shi Xuanling, Zhang Hong, Qiu Yan, He Zhongping, Wang Wei, Lian Gewei, Yin Xiaolei, Du Liying, … Ding Mingxiao  
*The Journal of Infectious Diseases* (2004-09) <https://doi.org/cgqj5b>   
DOI: [10.1086/423286](https://doi.org/10.1086/423286) · PMID: [15319862](https://www.ncbi.nlm.nih.gov/pubmed/15319862)

190. **Potent human monoclonal antibodies against SARS CoV, Nipah and Hendra viruses**   
Ponraj Prabakaran, Zhongyu Zhu, Xiaodong Xiao, Arya Biragyn, Antony S Dimitrov, Christopher C Broder, Dimiter S Dimitrov  
*Expert Opinion on Biological Therapy* (2009-04-08) <https://doi.org/b88kw8>   
DOI: [10.1517/14712590902763755](https://doi.org/10.1517/14712590902763755) · PMID: [19216624](https://www.ncbi.nlm.nih.gov/pubmed/19216624) · PMCID: [PMC2705284](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2705284)

191. **Prior Infection and Passive Transfer of Neutralizing Antibody Prevent Replication of Severe Acute Respiratory Syndrome Coronavirus in the Respiratory Tract of Mice**   
Kanta Subbarao, Josephine McAuliffe, Leatrice Vogel, Gary Fahle, Steven Fischer, Kathleen Tatti, Michelle Packard, Wun-Ju Shieh, Sherif Zaki, Brian Murphy  
*Journal of Virology* (2004-04-01) <https://doi.org/b8wr7c>   
DOI: [10.1128/jvi.78.7.3572-3577.2004](https://doi.org/10.1128/jvi.78.7.3572-3577.2004) · PMID: [15016880](https://www.ncbi.nlm.nih.gov/pubmed/15016880) · PMCID: [PMC371090](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC371090)

192. **The Effectiveness of Convalescent Plasma and Hyperimmune Immunoglobulin for the Treatment of Severe Acute Respiratory Infections of Viral Etiology: A Systematic Review and Exploratory Meta-analysis**   
John Mair-Jenkins, Maria Saavedra-Campos, J. Kenneth Baillie, Paul Cleary, Fu-Meng Khaw, Wei Shen Lim, Sophia Makki, Kevin D. Rooney, Jonathan S. Nguyen-Van-Tam, Charles R. Beck, Convalescent Plasma Study Group  
*Journal of Infectious Diseases* (2015-01-01) <https://doi.org/f632n7>   
DOI: [10.1093/infdis/jiu396](https://doi.org/10.1093/infdis/jiu396) · PMID: [25030060](https://www.ncbi.nlm.nih.gov/pubmed/25030060) · PMCID: [PMC4264590](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4264590)

193. **Identification of human neutralizing antibodies against MERS-CoV and their role in virus adaptive evolution**   
X.-C. Tang, S. S. Agnihothram, Y. Jiao, J. Stanhope, R. L. Graham, E. C. Peterson, Y. Avnir, A. S. C. Tallarico, J. Sheehan, Q. Zhu, … W. A. Marasco  
*Proceedings of the National Academy of Sciences* (2014-04-28) <https://doi.org/smr>   
DOI: [10.1073/pnas.1402074111](https://doi.org/10.1073/pnas.1402074111) · PMID: [24778221](https://www.ncbi.nlm.nih.gov/pubmed/24778221) · PMCID: [PMC4024880](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4024880)

194. **Exceptionally Potent Neutralization of Middle East Respiratory Syndrome Coronavirus by Human Monoclonal Antibodies**   
Tianlei Ying, Lanying Du, Tina W. Ju, Ponraj Prabakaran, Candy C. Y. Lau, Lu Lu, Qi Liu, Lili Wang, Yang Feng, Yanping Wang, … Dimiter S. Dimitrov  
*Journal of Virology* (2014-07-15) <https://doi.org/ggzf5p>   
DOI: [10.1128/jvi.00912-14](https://doi.org/10.1128/jvi.00912-14) · PMID: [24789777](https://www.ncbi.nlm.nih.gov/pubmed/24789777) · PMCID: [PMC4097770](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4097770)

195. **Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein**   
Alexandra C. Walls, Young-Jun Park, M. Alejandra Tortorici, Abigail Wall, Andrew T. McGuire, David Veesler  
*Cell* (2020-04) <https://doi.org/dpvh>   
DOI: [10.1016/j.cell.2020.02.058](https://doi.org/10.1016/j.cell.2020.02.058) · PMID: [32155444](https://www.ncbi.nlm.nih.gov/pubmed/32155444) · PMCID: [PMC7102599](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102599)

196. **Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus**   
Wenhui Li, Michael J. Moore, Natalya Vasilieva, Jianhua Sui, Swee Kee Wong, Michael A. Berne, Mohan Somasundaran, John L. Sullivan, Katherine Luzuriaga, Thomas C. Greenough, … Michael Farzan  
*Nature* (2003-11) <https://doi.org/bqvpjh>   
DOI: [10.1038/nature02145](https://doi.org/10.1038/nature02145) · PMID: [14647384](https://www.ncbi.nlm.nih.gov/pubmed/14647384) · PMCID: [PMC7095016](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7095016)

197. **The Role of ACE2 in Cardiovascular Physiology**   
Gavin Y. Oudit, Michael A. Crackower, Peter H. Backx, Josef M. Penninger  
*Trends in Cardiovascular Medicine* (2003-04) <https://doi.org/bsbp49>   
DOI: [10.1016/s1050-1738(02)00233-5](https://doi.org/10.1016/s1050-1738(02)00233-5)

198. **A human monoclonal antibody blocking SARS-CoV-2 infection**   
Chunyan Wang, Wentao Li, Dubravka Drabek, Nisreen M. A. Okba, Rien van Haperen, Albert D. M. E. Osterhaus, Frank J. M. van Kuppeveld, Bart L. Haagmans, Frank Grosveld, Berend-Jan Bosch  
*Cold Spring Harbor Laboratory* (2020-03-12) <https://doi.org/ggnw4t>   
DOI: [10.1101/2020.03.11.987958](https://doi.org/10.1101/2020.03.11.987958)

199. **Unexpected Receptor Functional Mimicry Elucidates Activation of Coronavirus Fusion**   
Alexandra C. Walls, Xiaoli Xiong, Young-Jun Park, M. Alejandra Tortorici, Joost Snijder, Joel Quispe, Elisabetta Cameroni, Robin Gopal, Mian Dai, Antonio Lanzavecchia, … David Veesler  
*Cell* (2019-02) <https://doi.org/gft3jg>   
DOI: [10.1016/j.cell.2018.12.028](https://doi.org/10.1016/j.cell.2018.12.028) · PMID: [30712865](https://www.ncbi.nlm.nih.gov/pubmed/30712865) · PMCID: [PMC6751136](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6751136)

200. **In Vitro Neutralization Is Not Predictive of Prophylactic Efficacy of Broadly Neutralizing Monoclonal Antibodies CR6261 and CR9114 against Lethal H2 Influenza Virus Challenge in Mice**   
Troy C. Sutton, Elaine W. Lamirande, Kevin W. Bock, Ian N. Moore, Wouter Koudstaal, Muniza Rehman, Gerrit Jan Weverling, Jaap Goudsmit, Kanta Subbarao  
*Journal of Virology* (2017-10-18) <https://doi.org/ggqbpt>   
DOI: [10.1128/jvi.01603-17](https://doi.org/10.1128/jvi.01603-17) · PMID: [29046448](https://www.ncbi.nlm.nih.gov/pubmed/29046448) · PMCID: [PMC5709608](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5709608)

201. **Potent human neutralizing antibodies elicited by SARS-CoV-2 infection**   
Bin Ju, Qi Zhang, Xiangyang Ge, Ruoke Wang, Jiazhen Yu, Sisi Shan, Bing Zhou, Shuo Song, Xian Tang, Jinfang Yu, … Linqi Zhang  
*Cold Spring Harbor Laboratory* (2020-03-26) <https://doi.org/ggp7t4>   
DOI: [10.1101/2020.03.21.990770](https://doi.org/10.1101/2020.03.21.990770)

202. **Human neutralizing antibodies against MERS coronavirus: implications for future immunotherapy**   
Xian-Chun Tang, Wayne A Marasco  
*Immunotherapy* (2015-07) <https://doi.org/ggqbpz>   
DOI: [10.2217/imt.15.33](https://doi.org/10.2217/imt.15.33) · PMID: [26098703](https://www.ncbi.nlm.nih.gov/pubmed/26098703) · PMCID: [PMC5068219](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5068219)

203. **A Potent and Broad Neutralizing Antibody Recognizes and Penetrates the HIV Glycan Shield**   
R. Pejchal, K. J. Doores, L. M. Walker, R. Khayat, P.-S. Huang, S.-K. Wang, R. L. Stanfield, J.-P. Julien, A. Ramos, M. Crispin, … I. A. Wilson  
*Science* (2011-10-13) <https://doi.org/bzqv8c>   
DOI: [10.1126/science.1213256](https://doi.org/10.1126/science.1213256) · PMID: [21998254](https://www.ncbi.nlm.nih.gov/pubmed/21998254) · PMCID: [PMC3280215](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3280215)

204. **Broadly Neutralizing Antibodies against HIV: Back to Blood**   
Amir Dashti, Anthony L. DeVico, George K. Lewis, Mohammad M. Sajadi  
*Trends in Molecular Medicine* (2019-03) <https://doi.org/ggqbpr>   
DOI: [10.1016/j.molmed.2019.01.007](https://doi.org/10.1016/j.molmed.2019.01.007) · PMID: [30792120](https://www.ncbi.nlm.nih.gov/pubmed/30792120) · PMCID: [PMC6401214](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6401214)

205. **Importance of Neutralizing Monoclonal Antibodies Targeting Multiple Antigenic Sites on the Middle East Respiratory Syndrome Coronavirus Spike Glycoprotein To Avoid Neutralization Escape**   
Lingshu Wang, Wei Shi, James D. Chappell, M. Gordon Joyce, Yi Zhang, Masaru Kanekiyo, Michelle M. Becker, Neeltje van Doremalen, Robert Fischer, Nianshuang Wang, … Barney S. Graham  
*Journal of Virology* (2018-04-27) <https://doi.org/ggqbpv>   
DOI: [10.1128/jvi.02002-17](https://doi.org/10.1128/jvi.02002-17) · PMID: [29514901](https://www.ncbi.nlm.nih.gov/pubmed/29514901) · PMCID: [PMC5923077](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5923077)

206. **Anti–spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection**   
Li Liu, Qiang Wei, Qingqing Lin, Jun Fang, Haibo Wang, Hauyee Kwok, Hangying Tang, Kenji Nishiura, Jie Peng, Zhiwu Tan, … Zhiwei Chen  
*JCI Insight* (2019-02-21) <https://doi.org/ggqbpw>   
DOI: [10.1172/jci.insight.123158](https://doi.org/10.1172/jci.insight.123158) · PMID: [30830861](https://www.ncbi.nlm.nih.gov/pubmed/30830861) · PMCID: [PMC6478436](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6478436)

207. **The antiviral effect of interferon-beta against SARS-Coronavirus is not mediated by MxA protein**   
Martin Spiegel, Andreas Pichlmair, Elke Mühlberger, Otto Haller, Friedemann Weber  
*Journal of Clinical Virology* (2004-07) <https://doi.org/cmc3ds>   
DOI: [10.1016/j.jcv.2003.11.013](https://doi.org/10.1016/j.jcv.2003.11.013) · PMID: [15135736](https://www.ncbi.nlm.nih.gov/pubmed/15135736)

208. **Coronavirus virulence genes with main focus on SARS-CoV envelope gene**   
Marta L. DeDiego, Jose L. Nieto-Torres, Jose M. Jimenez-Guardeño, Jose A. Regla-Nava, Carlos Castaño-Rodriguez, Raul Fernandez-Delgado, Fernando Usera, Luis Enjuanes  
*Virus Research* (2014-12) <https://doi.org/f6wm24>   
DOI: [10.1016/j.virusres.2014.07.024](https://doi.org/10.1016/j.virusres.2014.07.024) · PMID: [25093995](https://www.ncbi.nlm.nih.gov/pubmed/25093995) · PMCID: [PMC4261026](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4261026)

209. **A Randomised Double-blind Placebo-controlled Trial to Determine the Safety and Efficacy of Inhaled SNG001 (IFN-β1a for Nebulisation) for the Treatment of Patients With Confirmed SARS-CoV-2 Infection**   
Synairgen Research Ltd.  
*clinicaltrials.gov* (2020-08-25) <https://clinicaltrials.gov/ct2/show/NCT04385095>

210. **Synairgen to start trial of SNG001 in COVID-19 imminently**   
Synairgen plc press release  
(2020-03-18) <http://synairgen.web01.hosting.bdci.co.uk/umbraco/Surface/Download/GetFile?cid=23c9b12c-508b-48c3-9081-36605c5a9ccd>

211. **Synairgen announces positive results from trial of SNG001 in hospitalised COVID-19 patients**   
Synairgen plc press release  
(2020-07-20) <http://synairgen.web01.hosting.bdci.co.uk/umbraco/Surface/Download/GetFile?cid=1130026e-0983-4338-b648-4ac7928b9a37>

212. **Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial**   
Phillip D Monk, Richard J Marsden, Victoria J Tear, Jody Brookes, Toby N Batten, Marcin Mankowski, Felicity J Gabbay, Donna E Davies, Stephen T Holgate, Ling-Pei Ho, … Pedro MB Rodrigues  
*The Lancet Respiratory Medicine* (2021-02) <https://doi.org/ghjzm4>   
DOI: [10.1016/s2213-2600(20)30511-7](https://doi.org/10.1016/s2213-2600(20)30511-7) · PMID: [33189161](https://www.ncbi.nlm.nih.gov/pubmed/33189161) · PMCID: [PMC7836724](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7836724)

213. **Nebulised interferon beta-1a for patients with COVID-19**   
Nathan Peiffer-Smadja, Yazdan Yazdanpanah  
*The Lancet Respiratory Medicine* (2021-02) <https://doi.org/ftmj>   
DOI: [10.1016/s2213-2600(20)30523-3](https://doi.org/10.1016/s2213-2600(20)30523-3) · PMID: [33189160](https://www.ncbi.nlm.nih.gov/pubmed/33189160) · PMCID: [PMC7833737](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7833737)

214. **Effect of Intravenous Interferon β-1a on Death and Days Free From Mechanical Ventilation Among Patients With Moderate to Severe Acute Respiratory Distress Syndrome**   
V. Marco Ranieri, Ville Pettilä, Matti K. Karvonen, Juho Jalkanen, Peter Nightingale, David Brealey, Jordi Mancebo, Ricard Ferrer, Alain Mercat, Nicolò Patroniti, … for the INTEREST Study Group  
*JAMA* (2020-02-25) <https://doi.org/ghzkww>   
DOI: [10.1001/jama.2019.22525](https://doi.org/10.1001/jama.2019.22525) · PMID: [32065831](https://www.ncbi.nlm.nih.gov/pubmed/32065831)

215. **A Randomized Clinical Trial of the Efficacy and Safety of Interferon β-1a in Treatment of Severe COVID-19**   
Effat Davoudi-Monfared, Hamid Rahmani, Hossein Khalili, Mahboubeh Hajiabdolbaghi, Mohamadreza Salehi, Ladan Abbasian, Hossein Kazemzadeh, Mir Saeed Yekaninejad  
*Antimicrobial Agents and Chemotherapy* (2020-08-20) <https://doi.org/gg5xvm>   
DOI: [10.1128/aac.01061-20](https://doi.org/10.1128/aac.01061-20) · PMID: [32661006](https://www.ncbi.nlm.nih.gov/pubmed/32661006) · PMCID: [PMC7449227](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7449227)

216. **A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults (ACTT-3)**   
National Institute of Allergy and Infectious Diseases (NIAID)  
*clinicaltrials.gov* (2021-02-04) <https://clinicaltrials.gov/ct2/show/NCT04492475>

217. **Table 1, Cost-Comparison Table for Biologic Disease-Modifying Drugs for Rheumatoid Arthritis**   
National Center for Biotechnology Information, U. S. National Library of Medicine 8600 Rockville Pike, Bethesda MD, 20894 Usa  
(2015-08) <https://www.ncbi.nlm.nih.gov/books/NBK349513/table/T43/>

218. **A Cost Comparison of Treatments of Moderate to Severe Psoriasis**   
Cheryl Hankin, Steven Feldman, Andy Szczotka, Randolph Stinger, Leslie Fish, David Hankin  
*Drug Benefit Trends* (2005-05) <https://escholarship.umassmed.edu/meyers_pp/385>

219. **TNF-α inhibition for potential therapeutic modulation of SARS coronavirus infection**   
Edward Tobinick  
*Current Medical Research and Opinion* (2008-09-22) <https://doi.org/bq4cx2>   
DOI: [10.1185/030079903125002757](https://doi.org/10.1185/030079903125002757) · PMID: [14741070](https://www.ncbi.nlm.nih.gov/pubmed/14741070)

220. **Sanofi and Regeneron begin global Kevzara® (sarilumab) clinical trial program in patients with severe COVID-19**   
Sanofi  
(2020-03-16) <http://www.news.sanofi.us/2020-03-16-Sanofi-and-Regeneron-begin-global-Kevzara-R-sarilumab-clinical-trial-program-in-patients-with-severe-COVID-19>

221. **Sarilumab COVID-19 - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04327388>

222. **COVID-19: combining antiviral and anti-inflammatory treatments**   
Justin Stebbing, Anne Phelan, Ivan Griffin, Catherine Tucker, Olly Oechsle, Dan Smith, Peter Richardson  
*The Lancet Infectious Diseases* (2020-04) <https://doi.org/dph5>   
DOI: [10.1016/s1473-3099(20)30132-8](https://doi.org/10.1016/s1473-3099(20)30132-8) · PMID: [32113509](https://www.ncbi.nlm.nih.gov/pubmed/32113509) · PMCID: [PMC7158903](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7158903)

223. **Baricitinib as potential treatment for 2019-nCoV acute respiratory disease**   
Peter Richardson, Ivan Griffin, Catherine Tucker, Dan Smith, Olly Oechsle, Anne Phelan, Michael Rawling, Edward Savory, Justin Stebbing  
*The Lancet* (2020-02) <https://doi.org/ggnrsx>   
DOI: [10.1016/s0140-6736(20)30304-4](https://doi.org/10.1016/s0140-6736(20)30304-4) · PMID: [32032529](https://www.ncbi.nlm.nih.gov/pubmed/32032529) · PMCID: [PMC7137985](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7137985)

224. **Lilly Begins Clinical Testing of Therapies for COVID-19 | Eli Lilly and Company** <https://investor.lilly.com/news-releases/news-release-details/lilly-begins-clinical-testing-therapies-covid-19>

225. **Baricitinib Combined With Antiviral Therapy in Symptomatic Patients Infected by COVID-19: an Open-label, Pilot Study**   
Fabrizio Cantini  
*clinicaltrials.gov* (2020-04-19) <https://clinicaltrials.gov/ct2/show/NCT04320277>

226. **Design and Synthesis of Hydroxyferroquine Derivatives with Antimalarial and Antiviral Activities**   
Christophe Biot, Wassim Daher, Natascha Chavain, Thierry Fandeur, Jamal Khalife, Daniel Dive, Erik De Clercq  
*Journal of Medicinal Chemistry* (2006-05) <https://doi.org/db4n83>   
DOI: [10.1021/jm0601856](https://doi.org/10.1021/jm0601856) · PMID: [16640347](https://www.ncbi.nlm.nih.gov/pubmed/16640347)

227. **An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice**   
Timothy P. Sheahan, Amy C. Sims, Shuntai Zhou, Rachel L. Graham, Andrea J. Pruijssers, Maria L. Agostini, Sarah R. Leist, Alexandra Schäfer, Kenneth H. Dinnon, Laura J. Stevens, … Ralph S. Baric  
*Science Translational Medicine* (2020-04-29) <https://doi.org/ggrqd2>   
DOI: [10.1126/scitranslmed.abb5883](https://doi.org/10.1126/scitranslmed.abb5883) · PMID: [32253226](https://www.ncbi.nlm.nih.gov/pubmed/32253226) · PMCID: [PMC7164393](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164393)

228. **Antiviral Monoclonal Antibodies: Can They Be More Than Simple Neutralizing Agents?**   
Mireia Pelegrin, Mar Naranjo-Gomez, Marc Piechaczyk  
*Trends in Microbiology* (2015-10) <https://doi.org/f7vzrf>   
DOI: [10.1016/j.tim.2015.07.005](https://doi.org/10.1016/j.tim.2015.07.005) · PMID: [26433697](https://www.ncbi.nlm.nih.gov/pubmed/26433697) · PMCID: [PMC7127033](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7127033)

229. **Molecular biology of the cell**   
Bruce Alberts (editor)  
*Garland Science* (2002)   
ISBN: [9780815332183](https://worldcat.org/isbn/9780815332183)

230. **Intranasal Treatment with Poly(I{middle dot}C) Protects Aged Mice from Lethal Respiratory Virus Infections**   
J. Zhao, C. Wohlford-Lenane, J. Zhao, E. Fleming, T. E. Lane, P. B. McCray, S. Perlman  
*Journal of Virology* (2012-08-22) <https://doi.org/f4bzfp>   
DOI: [10.1128/jvi.01410-12](https://doi.org/10.1128/jvi.01410-12) · PMID: [22915814](https://www.ncbi.nlm.nih.gov/pubmed/22915814) · PMCID: [PMC3486278](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3486278)

231. **Main protease structure and XChem fragment screen**   
Diamond  
(2020-05-05) <https://www.diamond.ac.uk/covid-19/for-scientists/Main-protease-structure-and-XChem.html>