

SARS-CoV-2 and COVID-19: An Evolving Review of Diagnostics and Therapeutics

This manuscript ([permalink](#)) was automatically generated from [greenelab/covid19-review@4f4b409](#) on April 6, 2020.

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](#), or your own government.

Authors

- **Halie M. Rando**

 [0000-0001-7688-1770](#) ·  [rando2](#) ·  [tamefoxtime](#)

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)

- **Casey S. Greene**

 [0000-0001-8713-9213](#) ·  [cgreene](#) ·  [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 · Funded by the Gordon and Betty Moore Foundation (GBMF 4552)

- **Michael P. Robson**

 [0000-0002-4859-0033](#) ·  [mprobson](#)

Department of Computing Sciences, Villanova University, Villanova, Pennsylvania, United States of America

- **Simina M. Boca**

 [0000-0002-1400-3398](#) ·  [SiminaB](#)

Innovation Center for Biomedical Informatics, Georgetown University Medical Center, Washington, District of Columbia, United States of America

- **Nils Wellhausen**

 [0000-0001-8955-7582](#) ·  [nilswellhausen](#)

Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America

- **Ronan Lordan**

 [0000-0001-9668-3368](#) ·  [RLordan](#) ·  [el_ronan](#)

Institute for Translational Medicine and Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104-5158, USA

- **Christian Brueffer**

 [0000-0002-3826-0989](#) ·  [cbrueffer](#) ·  [cbrueffer](#)

Department of Clinical Sciences, Lund University, Lund, Sweden

- **Sadipan Ray**

 [0000-0002-9960-5768](#) ·  [rays1987](#)

Department of Systems Pharmacology & Translational Therapeutics, Perelman School of Medicine, University of

Pennsylvania, Philadelphia, PA 19104, USA; Institute for Translational Medicine and Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

- **Lucy D'Agostino McGowan**

 [0000-0001-7297-9359](#) ·  [LucyMcGowan](#) ·  [LucyStats](#)

Department of Mathematics and Statistics, Wake Forest University, Winston-Salem, North Carolina, United States of America

- **Anthony Gitter**

 [0000-0002-5324-9833](#) ·  [agitter](#) ·  [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

- **Anna Ada Dattoli**

 [0000-0003-1462-831X](#) ·  [aadattoli](#) ·  [aadattoli](#)

Department of Systems Pharmacology & Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

- **Ryan Velazquez**

 [0000-0002-3655-3403](#) ·  [rdvelazquez](#)

Azimuth1, McLean, VA

- **John P. Barton**

 [0000-0003-1467-421X](#) ·  [johnbarton](#) ·  [_jpbarton](#)

Department of Physics and Astronomy, University of California-Riverside, Riverside, California, United States of America

- **Jeffrey M. Field**

 [000-0001-7161-7284](#) ·  [Jeff-Field](#)

Department of Pharmacology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

Abstract

Since late 2019, Coronavirus disease 2019 (COVID-19) has spread around the world, resulting in the declaration of a pandemic by the World Health Organization (WHO). This infectious disease is caused by the newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Research on the virus SARS-CoV-2 and the disease it causes is emerging rapidly through global scientific efforts. The development of diagnostics, treatments, and vaccines will be critical to mitigating the impact of the virus. Here we present a collaborative effort to organize and consolidate the rapidly emerging scientific literature related to SARS-CoV-2. We present information about the virus in the context of what is known about related viruses and synthesize studies emerging about the diagnosis and treatment of COVID-19 alongside literature about related illnesses. A broad scientific effort to understand this pandemic and related viruses and diseases will be foundational to efforts to predict possible interventions. This text is an evolving and collaborative document that seeks to incorporate the ever-expanding body of information related to SARS-CoV-2 and COVID-19.

Where to Contribute

Introduce Yourself (GitHub Issue) <https://github.com/greenelab/covid19-review/issues/17>

Community Chat (Gitter Room) <https://gitter.im/covid19-review/community>

More Info (GitHub Readme) <https://github.com/greenelab/covid19-review#sars-cov-2-and-covid-19-an-evolving-review-of-diagnostics-and-therapeutics>

Introduction

General Background

On January 21, 2020, the World Health Organization (WHO) released its first report concerning what is now known as the Coronavirus disease 2019 (COVID-19) [1]. This infectious disease came to international attention on December 31, 2019 following an announcement by national officials in China about 44 cases of a respiratory infection of unknown cause. The first known cases were located in Wuhan City within the Hubei province of China, but the disease spread rapidly beyond Wuhan within China and subsequently around the world. At the time of the first situation report [1], 282 confirmed cases had been identified, primarily in China, but also 1-2 exported cases had been identified in several neighboring countries (Thailand, Japan, and the Republic of Korea). One week later, 4593 confirmed cases had been identified, spanning not only Asia, but also Australia, North America, and Europe [2]. On March 11, 2020, WHO formally classified the situation as a pandemic [3]. By WHO Situation Report 61, released on March 20, 2020, 266,073 confirmed cases had been reported worldwide, with cases on every continent except Antarctica [4]. At this time, over 11,000 deaths had been reported worldwide.

[Note: Maybe add a graph here, update as new reports come out.]

COVID-19 is caused by the newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a coronavirus, a family of RNA viruses known to cause respiratory and intestinal infections in humans and other species. Infectious diseases of global concern have previously been associated with coronaviruses, including Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) [5,6]; however, neither of these reached pandemic status, owing to proper containment procedures (SARS) or intrinsic limitations in virus transmission (MERS). Additionally, there are four endemic human coronaviruses that rarely progress beyond the mild symptoms associated with the common cold [6]. The precise identity of SARS-CoV-2 virus was unknown until approximately January 12, 2020, when Chinese officials released its genetic sequence to aid in worldwide efforts to diagnose the disease [1]. As researchers worldwide work to characterize SARS-CoV-2 and COVID-19, information about the transmission and life cycle of the virus as well as the diagnosis and treatment of the disease is emerging rapidly. In this review, we seek to consolidate information about the virus in the context of related viruses and to synthesize what is known about the diagnosis and treatment of COVID-19 and related diseases. This is a real-time, collaborative effort that welcomes submissions from scientists worldwide.

Coronaviruses: What are they, and what do we know about SARS-CoV-19?

Coronaviruses are RNA viruses that... [Summarize relevant mechanisms for cell entry & address evidence for/against ACE2 being important]

The origin of the SARS-CoV-19 virus is not yet fully understood. Genomic analyses and comparisons to other known coronaviruses suggest that SARS-CoV-19 is unlikely to have originated from a laboratory – either purposely engineered and released, or escaped – and instead evolved naturally in an animal host [7]. Among known coronaviruses, SARS-CoV-19 has the closest overall sequence similarity to RaTG13 (~96%) found in a *Rhinolophus affinis* bat [8], while the receptor binding domain (RBD) is highly similar to that of viruses found in pangolins [9]. This suggests that SARS-CoV-19 may have originated in viral reservoirs of similar hosts, however current evidence cannot discriminate an origin of the virus before or after zoonotic transfer to humans [7].

Mechanisms of Coronavirus-driven Disease in Humans

Coronaviruses are known to cause respiratory illnesses in humans through the following possible mechanisms...

Presentation of COVID-19

Information is rapidly becoming available about the wide range of symptoms that can be associated with COVID-19 as well as the range of symptom severity, onset from exposure, and possible risk or protective factors...

Vaccines for Viruses: Strategies for and challenges to development

What information is needed to develop a vaccine? How have vaccines for other viruses such as H1N1 been developed?

Diagnostics and Therapeutics for Viruses

Two major concerns within diagnosis include the detection of current infections in individuals with and without symptoms, and the detection of past exposure without an active infection. In the latter category, identifying whether individuals can develop or have developed sustained immunity is also a major consideration.

Within therapeutics, some possible efforts include efforts to identify strategies for the management of symptoms as well as the development of antivirals...

In this review, we seek to consolidate information about efforts to develop strategies for diagnosis and therapeutics as new information is released by the scientific community.

Pathogenesis

Mechanism of Host Infection by SARS-CoV-2

This section would also be great for the introduction of zoonotic diseases which has been shown to be the origin of SARS-CoV2.

Primary Transmission and Viral Entry

[How does SARS-CoV-2 enter human cells?] [What cells are primary infection sites for SARS-CoV-2?] [What structural aspects allow for viral entry?]

Viral Replication and Spreading

[Renamed section with transmission dynamics below] [Basic introduction into replication cycle] [What are the routes of transmission]

Reproduction Number and Dynamics of Transmission

Accurate estimates of the reproduction number of a virus are crucial to understanding the dynamics of infection and to predict the effects of different interventions. The basic reproduction number, R_0 , is the expected number of new infections caused by one infected person, assuming no time dependence and a wholly susceptible population [10]. The effective reproduction number, R_t , describes how the reproduction number may change over time, and is used to quantify deviations in R from R_0 , for example as some fraction of the population becomes infected, or as interventions are

put into place. R_0 and R_t can be estimated directly from epidemiological data or inferred using mathematical modeling. Modeling approaches are typically based upon a classic epidemiological model structure: the susceptible-infected-recovered (SIR) model and its extensions [11].

R_0 for COVID-19 is estimated to lie in the range $R_0=1.4-6.5$ [12,13,14]; estimates vary considerably depending on the data and the methods used. Most estimates currently derive from populations in Asia, since outbreaks in Europe and North America are more recent. Data-derived estimates (i.e. those that do not incorporate SIR-type models into their analysis) typically predict lower values of R_0 . For data-derived estimates, in one study of international cases, the predicted value is $R_0=1.7$ [15], in China (both Hubei province and nationwide), the value is predicted to lie in the range $R_0=2.0-3.6$ [12,16,17], and on a cruise ship where an outbreak occurred, predicted $R_0=2.28$ [18]. SIR model-derived estimates of R_0 range from 2.0 - 6.5 in China [19,20,21,22] to $R_0=4.8$ in France [23]. Using the same model as for the French population, this study estimated $R_0=2.6$ in South Korea [23], which is consistent with other studies [24]. From a meta-analysis of studies estimating R_0 , [13] predict the median as $R_0=2.79$.

Inference of the effective reproduction number can provide insight into how populations respond to an infection, and the effectiveness of interventions. In China, R_t was predicted to lie in the range 1.6-2.6 in Jan 2020, before travel restrictions [25]. R_t decreased from 2.35 one week before travel restrictions were imposed (Jan 23, 2020), to 1.05 one week after. Using their model, the authors also estimate the probability of new outbreaks occurring: the probability of a single individual exporting virus causing a large outbreak is 17-25% assuming MERS-like or SARS-like transmission, and the probability of a large outbreak occurring after ≥ 4 infections exist at a new location is greater than 50%. An independent study came to similar conclusions: in a two-week period before Jan 23 finding $R_t=2.38$, and decreasing to $R_t=1.34$ (using data from Jan 24 to Feb 3) or $R_t=0.98$ (using data from Jan 24 to Feb 8) [14]. In South Korea, R_t was inferred for Feb-Mar 2020 in two cities: Daegu (the center of the outbreak), and Seoul [24]. Metro data was also analyzed to estimate the effects of social distancing measures. R_t decreased in Daegu from around 3 to <1 over the period that social distancing measures were introduced. In Seoul, R_t decreased slightly, but remained close to 1 (and larger than R_t in Daegu). This highlights that social distancing measures appeared to work to contain the infection in Daegu, but that in Seoul, R_t remains above 1, thus secondary outbreaks are possible. It also shows the importance of region-specific analysis: the large decline in case load nationwide is mainly due to the Daegu region, and could hide persistence of the epidemic in other regions, such as Seoul and Gyeonggi-do. Similarly in Iran, estimates of R_t declined from 4.86 in the first week to 2.1 by the fourth week after the first cases in Iran were reported [26]. The authors attributed this decline to the effects of self-quarantine and government reductions in working time.

Immune Response to SARS-CoV-2

[Cellular responses to SARS-CoV-2 infection] [What is causing neutropenia and lymphopenia observed in COVID-19 patients] [Antibody production against SARS-CoV-2 by patient who recovered vs patient who did not recover] [Cytokines and other soluble factors contribution to immune response]

Systems level approaches for understanding SARS-CoV-2 pathogenesis

Systems biology provides a cross-disciplinary analytical platform integrating the different omics (genomics, transcriptomics, proteomics, metabolomics, and other omics approaches), bioinformatics, and computational strategies. These cutting-edge research approaches have enormous potential to study the complexity of biological systems and human diseases [27]. Over the last decade, systems biology approaches have been used widely to study the pathogenesis of diverse types of life-threatening acute and chronic infectious diseases [28]. Omics-based studies also provided meaningful information regarding host immune responses and surrogate protein markers in several viral, bacterial and protozoan infections [29].

The complex pathogenesis and clinical manifestations of SARS-CoV-2 infection are not understood adequately yet. A significant breakthrough in SARS-CoV-2 research was achieved through the successful full-length genome sequencing of the pathogen [8,30,31]. Multiple research groups have drafted the genome sequence of SARS-CoV-2 based on sequencing of clinical samples collected from bronchoalveolar lavage fluid (BALF) [8,30] or from BALF, throat swabs, or isolates of the virus cultured from BALF [31]. Importantly, SARS-CoV-2 has significant sequence homology with SARS-CoV (about 79%) and also to some extent with MERS-CoV (about 50%) [31]. However, a higher level of similarity (about 90%) has been observed between SARS-CoV-2 and bat-derived SARS-like coronaviruses (bat-SL-CoVZC45 and bat-SL-CoVZXC21), indicating a possible origin in bats [8,31].

The genome sequence of the pathogen subsequently allowed its phylogenetic characterization and prediction of its protein expression profile, which is crucial for understanding the pathogenesis and virulence of this novel viral infection. Availability of the genome sequence of SARS-CoV-2 enhances the potential for subsequent proteome-level studies to provide further mechanistic insights into the virus' complex pathogenesis. Of note, the cryo-electron microscopy structure of the SARS-CoV-2 spike (S) glycoprotein, which plays an important role in the early steps of viral infection, was reported very recently [32]. Even though no comprehensive proteomic analysis of the pathogen or of patients suffering from its infection has yet been reported, one forthcoming study has demonstrated SARS-CoV-2 infected host cell proteomics using human Caco-2 cells as an infection model [33]. The authors observed SARS-CoV-2 induced alterations in multiple vital physiological pathways, including translation, splicing, carbon metabolism and nucleic acid metabolism in the host cells.

There is a high level of sequence homology between SARS-CoV-2 and SARS-CoV, and sera from convalescent SARS-CoV patients might show some efficacy to cross-neutralize SARS-CoV-2-S-driven entry [34]. However, despite the high level of sequence homology, certain protein structures might be immunologically distinct, prohibiting effective cross-neutralization across different SARS strains [35]. Consequently, earlier proteome-level studies on SARS-CoV can also provide some essential information regarding the new pathogen [36,37]. Considering the paucity of omics-level big data sets for SARS-CoV-2 up until now, existing data hubs that contain information for other coronaviruses such as UniProt, NCBI Genome Database, The Immune Epitope Database and Analysis Resource (IEDB), and The Virus Pathogen Resource (ViPR) will serve as useful resources for computational and bioinformatics research on SARS-CoV-2.

Diagnostics

Current Strategies for Diagnosing COVID-19 and Similar Viral Infections

Given the heterogeneity of symptom presentation across patients with COVID-19, the development of standardized protocols for testing samples for SARS-CoV-2 is urgent. Following the release of the genetic sequence of the virus by Chinese officials on January 12, 2020, the first tests for detecting the virus were released on XX, 2020. These tests used the following approach to identify the active virus in patient samples... However, many countries have struggled to acquire the tests required to keep pace with the epidemic. [Why is it so difficult to scale up testing? What are some of the considerations?]

Possible Alternatives to Current Practices for Identifying Active Cases

[Are there other approaches that have worked for diagnosing other viruses at a rapid pace in large numbers of people?] [What are some approaches people are currently testing for detecting live viruses, especially SARS-CoV-2?]

Detection of Past Exposure and/or Sustained Immunity

[What are approaches that allow us to detect past exposure for other viruses?] [What efforts are underway to develop similar approaches for SARS-CoV-2?] [What is sustained immunity and what are the indicators?]

Limitations to Implementation of Large-Scale Testing

[Right now, reagent supply is an issue. Are there others concerns that are likely to emerge?]

Strategies and Considerations for Determining Whom to Test

[If it's not possible to test everyone, what strategies exist for selecting who to test?] [Are these strategies likely to change over time? Presumably there are different stages of managing spread vs mitigating severity once it's already at high prevalence?]

Therapeutics

Given the rapid predicted spread of the disease, the development of therapeutics will be critical to mitigating its effect on health and the mortality rate. Typically, therapeutics can take a few forms. First, the treatment and reduction of symptoms can result in the reduction of the severity and risk associated with an active infection. Second, the development of antiviral drugs can drive a reduced recovery time for patients by inhibiting the development of the virus once an individual is infected. Finally, vaccines present a strategy for bolstering the immune response of the population broadly to the virus, resulting in a lower rate of infection. All three of these strategies have been valuable elements of responses to other viruses, including coronaviruses, and are being investigated by researchers at present. Additionally, there have been suggestions within the scientific community that nutraceutical or dietary supplement interventions may prime an individual's immune system to prevent or lessen the impact of RNA virus infections [38,39]. In the following sections, we critically appraise the literature surrounding the repurposing of existing treatments and development of novel therapeutics for the prevention, mitigation, and treatment of coronavirus infections.

Treatment of Symptoms

The clinical picture of SARS-CoV-2 infection differs dramatically between individuals. Some are asymptomatic. Others experience mild COVID-19 symptoms, such as cough, sore throat and fever, while the most severe cases of COVID-19 include severe complications including pneumonia and Acute Respiratory Distress Syndrome (ARDS), which can lead to respiratory failure and death [40]. Vaccines are one avenue to mitigate harm from viral pathogens, but in the case of a rapidly growing pandemic the longer timeframe of vaccine development and distribution means that there can be a key for treatments that palliate symptoms to avoid the most severe outcomes from infection.

Tocilizumab

A recent study carried out on a sample of 191 adult COVID-19 in-patients at two Wuhan hospitals found that blood samples taken at admission contained significantly higher concentrations of interleukin-6 (IL-6) in patients who ultimately deceased compared to those who survived; average concentrations of IL-6 remained higher in the deceased group than the surviving group throughout hospitalization [41]. This suggests that these individuals may be experiencing a "cytokine storm", which refers to an excessive inflammatory response. IL-6 plays a key role in this response [42]. IL-6 is a pro-inflammatory cytokine belonging to the family of interleukins, which are immune system regulators that are primarily responsible for immune cell differentiation. Specifically, IL-6 promotes the differentiation of activated B cells into immunoglobulin-producing plasma cells [43] and acts as a growth factor for hybridoma and myeloma cells [44,45]. In addition, IL-6 also induces the

differentiation of naïve CD4⁺ T cells into effector T-cell subsets [46]. In this way interleukins regulate both the pro- and anti-inflammatory responses. In this context, the observation of elevated IL-6 in patients who died may reflect an over-production of proinflammatory interleukins.

In a healthy situation the lung respiratory epithelium together with alveolar macrophages limits the activation of the immune system, ensuring homeostasis. The introduction of the S-protein from SARS-CoV to mouse macrophages was found to increase production of IL-6 and TNF- α [47], and deceased SARS-CoV patients were found to have intermediate levels of IL-6, IL-1 β , and TNF- α expressed in a number of ACE2-expressing cell types sampled from the lung and bronchial tissues during autopsy [48]. However, other reports found the severe respiratory condition ARDS to be associated with elevated concentrations of IL-6 in BALF, but that concentrations of Tumor Necrosis Factor α (TNF- α) and IL-1 β decreased with the onset of ARDS [49]. These cytokines enhance the pro-inflammatory reaction by increase acute-phase signaling, trafficking of immune cells to the site of primary infection, epithelial cell activation, and secondary cytokine production. The acute phase response to infection results in the heavily damage of the endothelium of blood vessels, which disrupts the balance between pro and anti-inflammatory response [49]. Thus, the holes generated allow not just for the passage of neutrophils, macrophages and lymphocytes to the site of the infection but also the accumulation of liquids into the lungs, which is the ultimate cause of the death as per Acute Distress Respiratory Syndrome (ARDS) or Severe Acute Respiratory Syndrome (SARS) [50], also caused by the new coronavirus. Recently Chinese and Italian doctors have found that the the Tocilizumab (actemra, by Roche), a drug commonly used in the rheumatoid arthritis, may palliate the most severe symptoms associated with COVID-19.

Anticipated Mechanism

Human IL-6 is a glycoprotein of 26 kDa and it consists of 184 amino acids containing 2 potential N-glycosylation sites and four cysteine residues. IL-6 binds to its receptor either in the insoluble (IL-6R) and soluble (sIL-6R) form. The receptor specificity determines the type of signaling. Specifically, the binding of IL-6 to the cell membrane receptor IL-6R gives rise to the “classical transduction of the signaling”, while to binding to sIL-6R generate the so called “trans-signaling” [51,52]. IL-6 signaling occurs through 3 independent pathways: the Janus-activated kinase (JAK)-STAT3 pathway, the Ras/Mitogen-Activated Protein Kinases (MAPK) pathway and the Phosphoinositol-3 Kinase (PI3K)/Akt pathway [53]. The ultimate result of the IL-6 cascade is to direct transcriptional activity of various promoters of pro-inflammatory cytokines, such as IL-1 and TFN, including IL-6 own regulation through the activity of NF- κ B [53]. Particularly, IL-6 synthesis is tightly regulated both transcriptionally and post-transcriptionally. In this context, it has been shown that viral proteins can enhance transcription of the IL-6 gene, via strengthening the DNA-binding activity between several transcriptional factors and IL-6 gene-cis-regulatory elements [54]. Tocilizumab is a humanised monoclonal antibody that binds both to the insoluble and soluble receptor of IL-6, de facto inhibiting the IL-6 immune cascade.

Current Evidence

Chinese doctors have started a trial enrolling 188 patients of which 14 with severe lung disease have shown clear sings of improvements, according to their results [55]. Also, The AIFA (the Italian Drug Agency) approved the start of a new trial on March 19 recruiting patients at the initial stage of the infection [56]. Together with these independent trials, Roche, also in collaboration with the FDA, will start a randomised, double-blind, placebo-controlled phase III trial early April. The trial will enroll 330 patients globally, which will be followed for 60 days upon use of the drug via injection to analyse its efficiency/safety (Biopharma-reporter.com). However, previous studies on RA showed that in patients treated with TCZ the rate of incident infections in clinical practice patients was higher than the one observed during clinical trial [57]. Also, RA patients with chronic hepatitis B (HB) infection showed high risk of HB virus reactivation upon TCZ administration in combination with other RA drugs [58]. These last findings highlight the need to search for a balance between impairing a harmful immune response, such as the one generated by the cytokine storm, and preventing the worsening of the

clinical picture of the patients by potential new viral infections. This aspect is probably crucial to be investigated further in the trials that are about to start. Perhaps, the TCZ treatment would best suit patients with severely compromised lungs due to the Covid-19 infection and are therefore at greater risk of death, in order to stop the uncontrolled immune response before it's too late.

Summary

Summarize the state of the symptom management approach.

Small Molecule Drugs for Targeting SARS-CoV-2

The replication cycle of a virus within an epithelial host cell includes 6 basic steps which can be shortly summarised as follow: i) attachment of the virus to the host cell; ii) penetration by endocytosis; iii) uncoating, classically defined as the release of viral contents into the host cell; iv) biosynthesis, during which the viral genetic material enters the nucleus where it gets replicated; v) assembly, where viral proteins are translated and new viral particles are assembled; vi) release, when the new viruses are released into the extracellular environment [59]. Antiviral drugs do not kill the virus, rather they inhibit its amplification by impairing one of these steps. Nowadays, many of these drugs act during the biosynthesis step in order to inhibit the virus' genetic material replication. Importantly, SARS-CoV-2 is an RNA virus. Differently from a DNA virus, which can use the host enzymes to propagate itself, RNA viruses depends on their own polymerase, the RNA-dependent RNA polymerase (RdRP), in order to be replicated [60,61].

Nucleotide Analogs

Why one might use nucleotide analogs.

Avigan

Avigan (Flavipiravir, from Toyama chemical Fujifilm) is a drug which has been found effective to block viral amplification in the Influenza virus infection.

Anticipated Mechanism

Specifically, Avigan is a nucleoside precursor efficiently recognised as guanosine and adenosine analogue by the virus polymerase (RNA-dependent RNA polymerase). While a single incorporation does not influence RNA transcription, multiple events of incorporation lead to the arrest of RNA synthesis [62]. Importantly It was already shown that Avigan is able to give 100% coverage against the Ebola virus in mice [63]. Furthermore, there are evidences that drug might also work against Corona virus infection. For instance, a recent study showed its effectiveness compared to other antivirals such as lopinavir and ritonavir [64]. The drug was tested on a sample of 80 patients (35 experimental sample, 45 control group) and increased the speed of recovery (measured as viral clearance from the patient by RT-PCR) of about 4 days, compared to the control sample treated with the other anti-virals, such as Lopinavir and Ritonavir. Also lung body scan seem to look better in about 91% of the patients analysed [64]. However, the size of the sample is too small to give a powerful statistics, as well as the choice of the patients did not take into consideration important factors such as previous clinical conditions, sex, while there was no age categorisation.

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the antiviral approach.

Remdesivir

Remdesivir (GS-5734) was developed by Gilead Sciences to treat Ebola. It does not have any FDA-approved use. Although a clinical trial in the Democratic Republic of Congo found some evidence of effectiveness against ebola, two antibody preparations were found to be more effective, and Remdesivir was not pursued [65].

Anticipated Mechanism

Remdesivir is metabolized to GS-441524, an adenosine analog that inhibits a broad range of polymerases and then evades exonuclease repair causing chain termination [66,67,68]. Although it was developed against Ebola, it also inhibits the MERS-CoV and SARS-CoV polymerase and inhibits coronavirus replication in cell culture assays with submicromolar IC50s [69]. It also inhibits SARS-CoV-2, showing synergy with chloroquine [68].

Current Evidence

In addition to the previous work showing Remdesivir to be an effective treatment for viral pathogens such as SARS-CoV and MERS-CoV in cultured cells and animal models, a recent study found that administration of Remdesivir to non-human primate models resulted in 100% protection against infection by the Ebola virus. Remdesivir has also been reported to inhibit SARS-CoV-2 infection in a human cell line sensitive to the virus [68].

The effectiveness of Remdesivir for treating patients with COVID-19 is currently under investigation. Remdesivir has been used on some COVID-19 patients under compassionate use guidelines [70,71]. All were in late stages of COVID-19 infection, and these reports are inconclusive about the drug's efficacy. Remdesivir recently entered controlled clinical trials, and as of March 2020, there are six clinical trials underway to treat COVID-19 patients at both early and late stages of infection and in combinations with other drugs [??? 10.1038/s41422-020-0282-0,73,74,75,76,77,78].

Summary

Remdesivir is a major drug candidate since it attacks the virus with high potency and known mechanism. Moreover, one of the most successful therapies 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 HIV and Herpes. Note that the HIV and Herpes polymerases are a reverse transcriptase and a DNA polymerase respectively, whereas SARS-CoV-2 encodes an RNA dependent RNA polymerase, 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.

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the antiviral approach.

Protease Inhibitors

Why it may be useful

Protease Inhibitor 1

Anticipated Mechanism

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the antiviral approach.

Molecules Targeting the Viral Envelope

Why it may be useful

Viral Envelope Targeter 1

Anticipated Mechanism

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the antiviral approach.

Drugs Targeting Host Proteins

Brief background on the therapeutic.

Drug (or drug class) 1

Viral Entry Receptors

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the antiviral approach.

Broad-Spectrum Pharmaceuticals

Hydroxychloroquine

Nutraceuticals

Considering the current pandemic, scientists and the medical community are scrambling to repurpose or discover novel host-directed therapies for which nutraceuticals hold some promise. Nutraceuticals are classified as supplements with health benefits beyond their basic nutritional value designed for the prophylaxis and treatment of disease [79,80]. Nutraceuticals purported to boost the immune response, reduce immunopathology, exhibit antiviral activities or prevent acute respiratory distress syndrome (ARDS) are being considered for their potential therapeutic value [39]. A host of potential candidates have been highlighted in the literature that target various aspects of the COVID-19 viral pathology, while others are thought to prime the host immune system. These candidates include vitamins and minerals along with extracts and omega-3 polyunsaturated fatty acids (n-3 PUFA) [81]. Considerable evidence in vitro and in vivo suggests that nutraceuticals containing phycocyanobilin, N-acetylcysteine, glucosamine, selenium or phase 2 inductive nutraceuticals (e.g. ferulic acid, lipoic acid, or sulforaphane) can prevent or modulate RNA virus infections via amplification of the signaling activity of mitochondrial antiviral-signaling protein (MAVS) and activation of toll-like receptor 7 (TLR7) [38]. While promising, further animal and human studies are required to assess the therapeutic potential of these various nutraceuticals against COVID-19.

n-3 PUFA

Another potential nutraceutical that has exhibited beneficial effects against various viral infections is n-3 PUFA [81], such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA intake can come from a diet high in fish intake or through dietary supplementation with fish oils or purified oils [82].

Potential Mechanisms

N-3 PUFA nutraceuticals can mediate inflammation and they have the capacity to modulate the adaptive immune response [80,82,83]. Another potential mechanism by which n-3 PUFA could exert beneficial effects against viral infections is by acting as precursor molecules for the biosynthesis of endogenous specialised proresolving mediators (SPM) like protectins and resolvins that actively resolve inflammation and infection [84].

Current Evidence

SPM have exhibited beneficial effects against a variety of lung infections including RNA viruses [85]. Indeed, protectin D1 has been shown to increase survival from H1N1 viral infection in mice by affecting the viral replication machinery [86]. Moreover, not all studies are in agreement that n-3 PUFA are effective against infections [87]. Indeed, the effectiveness of n-3 PUFA against infections is dependent on the dosage, timing, and the specific pathogens responsible [88].

Summary

However, the overall lack of human studies in this area means there is limited evidence as to whether these nutraceuticals could affect COVID-19 infection.

Zinc Supplements

There is evidence that nutrient supplements may exhibit some benefit against RNA viral infections. Zinc is a trace metal obtained from dietary sources or supplementation that is important for the maintenance of immune cells involved in adaptive and innate immunity [89]. Zinc supplements can be administered orally as a tablet or as a lozenge and they are available in many forms such zinc picolinate, zinc acetate, and zinc citrate. Zinc is also available from dietary sources including meat, seafood, nuts, seeds, legumes, and dairy.

Potential Mechanisms

The role of zinc in immune function has been extensively reviewed [89]. Zinc is an important signaling molecule and zinc levels can alter host defense systems. In inflammatory situations such as an infection, zinc can regulate leukocyte immune responses and it can activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), thus altering cytokine production [90,91]. In particular, zinc supplementation can increase natural killer cell levels, which are important cells for host defense against viral infections [89,92].

Current Evidence

Adequate zinc intake has been associated with reduced incidence of infection [93] and antiviral immunity [94]. Similarly, a randomized, double-blind, placebo-controlled trial that administered zinc supplementation to elderly subjects over the course of a year found zinc deficiency to be associated with increased susceptibility to infection and that zinc deficiency could be prevented through supplementation [93]. Clinical trial data supports the utility of zinc to diminish the duration and severity of symptoms associated with common colds when it is provided within 24 hours of the onset of symptoms [95,96]. In coronaviruses specifically, in vitro evidence demonstrates that the combination of zinc (Zn²⁺) and zinc ionophores (pyrithione) can interrupt the replication mechanisms of SARS-CoV-GFP (a fluorescently tagged SARS-CoV) and a variety of other RNA viruses [97,98].

Summary

While overall there is encouraging data for zinc supplementation against the common cold and viral infections, there is currently limited evidence to suggest zinc supplementation has any beneficial effects against the current novel COVID-19, thus further research is imperative. However, it would be advisable to maintain a healthy diet to ensure an adequate zinc status to prevent the likelihood of an infection.

Vitamin C

Vitamins B, C, D, and E have also been suggested as potential nutrient supplement interventions for COVID-19 [81,99]. In particular vitamin C has been proposed as a potential prophylactic and therapeutic agent against COVID-19. Vitamin C can be obtained via dietary sources such as fruit and vegetable or via supplementation.

Potential Mechanisms

Vitamin C plays a significant role in promoting immune function due to its effects on various immune cells. Vitamin C affects inflammation by modulating cytokine production, decreasing histamine levels, enhancing the differentiation and proliferation of T- and B-lymphocytes, increasing antibody levels, and protecting against the negative effects of reactive oxygen species amongst other effects [100,101,102]. During viral infections vitamin C is utilised as evinced by lower concentrations in leukocytes and lower concentrations of urinary vitamin C. Post-infection, these levels return to baseline ranges [???,103,104,105,106].

Current Evidence

A recent meta-analysis found consistent support for regular vitamin C supplementation reducing the duration of the common cold, but that supplementation with vitamin C (> 200 mg) failed to reduce the incidence of colds [107]. Individual studies have found Vitamin C to reduce the susceptibility of patients to lower respiratory tract infections such as pneumonia [108]. A recent meta-analysis has demonstrated in twelve trials that vitamin C supplementation reduced the length of stay of patients in intensive care units (ICUs) by 7.8% (95% CI: 4.2% to 11.2%; p = 0.00003). Furthermore, high doses (1-3 g/day) significantly reduced the length of an ICU stay by 8.6% in six trials (p = 0.003). Vitamin C also shortened the duration of mechanical ventilation by 18.2% in three trials in which patients required

intervention for over 24 hours (95% CI 7.7% to 27%; $p = 0.001$) [[109](#)]. Despite these findings, the CITRUS ALI study failed to show a benefit of a 96-hour infusion of vitamin C to treat ARDS, which is a severe complication of COVID-19 infection [[110](#)].

Summary

The evidence suggests that vitamin C supplementation can shorten the duration of a cold, reduce an individual's susceptibility to infections, and shorten a patient's stay in ICU when administered at high doses. While there is anecdotal evidence from China and the United States that vitamin C is currently being used for the treatment of COVID-19, further controlled research is required.

Vitamin D

In terms of other dietary supplements, vitamin D can modulate the adaptive and innate immune system and has been associated with various aspects of health. Vitamin D can be sourced through diet or supplementation, but it is mainly biosynthesised by the body on exposure to sunlight.

Potential Mechanisms

Vitamin D deficiency is associated with an increased susceptibility to infection [???]. In particular, vitamin D deficient patients are at risk of developing acute respiratory infections [???] and ARDS [[111](#)]. 1,25-dihydroxyvitamin D3 is the active form of vitamin D that is involved in adaptive and innate responses, whereby the vitamin D receptor is expressed in various immune cells and vitamin D is an immunomodulator of antigen presenting cells, dendritic cells, macrophages, monocytes, and T- and B-lymphocytes [???,[112](#)]. Due to its potential immunomodulating properties, vitamin D supplementation may be advantageous to maintain a healthy immune system.

Current Evidence

A recent preprint postulated that an individual's vitamin D status may significantly affect one's risk of developing COVID-19. This hypothesis was derived from the fact that the current pandemic occurred in winter in Wuhan China when 25-hydroxyvitamin D concentrations are at their lowest due to lack of sunlight, whereas in the Southern Hemisphere, where it was nearing the end of the summer, the number of cases was low at that time coinciding with higher 25-hydroxyvitamin D concentrations [[113](#)]. The authors suggest that people at risk of developing COVID-19 should increase their vitamin D3 intake to reach 25-hydroxyvitamin D plasma concentrations above 40–60 ng/ml. The authors also suggest supplementation of vitamin D to treat infected patients and to prevent infection in hospital staff. While vitamin D is relatively inexpensive and safe to consume, caution is warranted when interpreting this review as it has yet to be determined whether vitamin D levels effect COVID-19 specifically. Likewise, it is assumed that COVID-19 may be seasonal, but there are multiple other factors at play that can affect vitamin D levels that need to be considered. These factors include an individual's nutritional status, their age, their occupation, skin pigmentation, potential comorbidities, and the variation of exposure to sunlight due to latitude amongst others [[114](#)].

Summary

Supplementation of vitamin D and maintaining a healthy diet for optimum vitamin D status warrants further investigation. This is particularly important considering 'stay in place' guidance has been implemented in many densely populated cities around the world. This measure is likely to limit people's exposure to sunlight and thus reduce endogenous synthesis of vitamin D, potentially weakening the immune system and increasing the risk of COVID-19 infection.

Nutraceutical Conclusions

Despite all the potential benefits of nutraceutical and dietary supplement interventions presented, currently there is a paucity of clinical evidence to support their use for the prevention or mitigation of COVID-19 infections. Nevertheless, optimal nutritional status will undoubtedly prime an individual's immune system to protect against the effects of acute respiratory viral infections by supporting normal maintenance of the immune system [115]. Overall, supplementation of vitamin C, vitamin D, and zinc may be an effective method of ensuring their adequate intake to maintain optimal immune function, which may also convey beneficial effects against viral infections due to their immunomodulatory effects. However, many supplements and nutraceuticals designed for various ailments are available in the United States and beyond that are not strictly regulated [116]. Indeed, there can be safety and efficacy concerns associated with many of these products. Often, the vulnerable member of society can be exploited in this regard and unfortunately the COVID-19 pandemic is no different. The Food and Drug Administration (FDA) has issued warnings to several companies for advertising falsified claims in relation to the preventative and therapeutic capabilities of their products against COVID-19 [117].

In light of these serious occurrences, it is pertinent to clarify that the nutraceuticals discussed in this review have been selected because of their possible relevance to the biological mechanisms that can beneficially affect viral and respiratory infections. Therefore, further intensive investigation is required to establish the effects of these nutraceuticals, if any, against COVID-19.

Biological Drugs for COVID-19

Neutralizing Antibodies

Monoclonal antibodies (mAbs) have revolutionized the way we treat human diseases. As a result, they have become some of the best-selling drugs in the pharmaceutical market in recent years [??? 10.1186/s12929-019-0592-z]. There are currently 79 FDA approved mAbs on the market including antibodies for viral infections (e.g. Ibalizumab for HIV and Palivizumab for RSV) [118,119]. Although vaccines remain the most important way to prevent viral infections, their development process is long and they fail to provide immediate prophylactic protection or treat ongoing infections [120]. For that reason, neutralizing antibodies have emerged to address these shortcomings. Virus-specific neutralizing antibodies commonly target viral surface glycoproteins or host structures, thereby inhibiting viral entry through receptor binding interference [121,122]. This section discusses current efforts in developing neutralizing antibodies against SARS-CoV-2 and how expertise gained from previous approaches for MERS-CoV and SARS-CoV may benefit antibody development.

Spike (S) Neutralizing Antibody

During the first SARS epidemic in 2002, nAbs were found in SARS-CoV infected patients [???,123]. Several studies following up on these findings identified various S glycoprotein epitopes as the major targets of neutralizing antibodies against SARS-CoV [124]. The passive transfer of immune serum containing nAbs from SARS-CoV-infected mice resulted in protection of naïve mice from viral lower respiratory tract infection upon intranasal challenge [125]. Similarly, a meta-analysis suggested that administration of plasma from recovered SARS-CoV patients reduced mortality upon SARS-CoV infection [126].

Similar results have been observed for MERS-CoV infections, which emerged as the second coronavirus-related epidemic. Neutralizing antibodies have been identified against various epitopes of the RBD of the S glycoprotein [127; doi:10.1128/JVI.00912-14].

Spike (S) Neutralizing Antibody Anticipated Mechanisms

Coronaviruses use trimeric spike (S) glycoproteins on their surface to bind to host cell receptors, such as ACE2, allowing for cell entry [34; doi:10.1016/j.cell.2020.02.058]. Each S glycoprotein protomer is comprised of an S1 domain, also called the receptor binding domain (RBD), and an S2 domain. The S1

domain binds to host cell receptors while the S2 domain facilitates the fusion between the viral envelope and host cell membranes [124]. Although targeting of the host cell receptor ACE2 shows efficacy in inhibiting SARS-CoV-2 infection [128], given the physiological relevance of ACE2 [129], it would be favorable to target virus-specific structures rather than host receptors. This forms the rationale of developing neutralizing antibodies against the S glycoprotein, disrupting its interaction with ACE2 and other receptors and thereby inhibiting viral entry.

Spike (S) Neutralizing Antibody Current Evidence

The first human neutralizing antibody against SARS-CoV-2 targeting the trimeric spike (S) glycoproteins has been developed using hybridoma technology, [130], 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 and SARS-CoV2 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 [130,131]. 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 [132]. 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 [35]. Interestingly, the patient isolated antibodies did not cross-react with RBD's from SARS-CoV and MERS-CoV, although cross-reactivity to the trimeric spike proteins of SARS-CoV and MERS-CoV was observed. This 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 nAbs therapy due to selective pressure from neutralizing antibodies [133,134]. 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 [135]. For MERS-CoV, a combination of multiple neutralizing antibodies targeting different antigenic sites prevented neutralization escape [136]. 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 [35]. 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 neutralizing antibodies can be drawn at this point. Rather, higher neutralizing antibody 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 [137].

Spike (S) Neutralizing Antibody Summary

Results from the SARS-CoV and MERS-CoV epidemics can provide valuable lessons for the design of neutralizing antibodies for the current outbreak. The findings for SARS-CoV and MERS 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 [136]. 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 [137]. These findings underscores our current lack of understanding the full immune response to SARS-CoV-2.

Anticipated Mechanism

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the neutralizing antibody approach.

Interferons

Interferons (IFNs) are a family of cytokines crucial to activate the first (innate) immune system response against viral infections. Interferons are classified into three categories based on their receptor specificity: type I, II and III [42]. Specifically, IFNs I (IFN- α and β) and II (IFN- γ) induce the expression of antiviral proteins which bring the viral RNA to degradation [138]. Among these IFNs, IFN- β was already found to strongly inhibit the replication of other corona viruses, such as SARS-Cov, in cell culture, while IFN- α and γ were shown to be less effective in this context [138]. There are evidences that patients with higher susceptibility to develop Acute respiratory distress syndrome (ARDS) show indeed deficiency of IFN- β . For instance, upon other Corona viruses infection IFN- β expression and synthesis is impaired, so that the virus can in fact escape the innate immune response [139].

On March 18 2020 Synairgen plc has received approval to start a phase II trial for SNG001, an IFN- β -1a formulation to be delivered to lungs via inhalation. SNG001 was already shown to be effective reducing viral load in swine flu in vivo model, as well as it has been shown to be effective in the protection from other Corona virus infection in vitro (Synairgen plc, press release).

Anticipated Mechanism

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of interferons.

Vaccines

Vaccines, widely recognized as one of the most significant advances in human health during the 20th century, can be used to bolster both individual and herd immunity to a virus by promoting the development of antibodies without infection. [Are vaccines available for other coronaviruses or related viral illnesses?] [What are some of the challenges to developing a vaccine? What needs to be taken into account about how the virus works?] [Are there any challenges or opportunities unique to coronaviruses and/or SARS-CoV-2?] [What are some approaches being tested or considered?]

DNA Vaccines

Brief background on the therapeutic.

Anticipated Mechanism

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the vaccine approach.

RNA Vaccines

Brief background on the therapeutic.

Anticipated Mechanism

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the vaccine approach.

Viral Particle Vaccines

Brief background on the therapeutic.

Anticipated Mechanism

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the vaccine approach.

Oligonucleotide Therapies

Background

Anticipated Mechanism

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the neutralizing antibody approach.

Methods

Article Selection and Evaluation

The authors solicited relevant articles to be submitted via [GitHub](#) for review. Articles were classified as *diagnostic*, *therapeutic*, or *other*. Following a framework often used for assessing medical literature, the review consisted of examining the methods used in the article, the assignment (whether the study was observational or randomized), the assessment, the results, the interpretation, and how well the study extrapolates [[140](#)].

Diagnostic Papers

Methods

Reviewers began by describing the study question(s) being investigated by the article. They then described the study population, the sample size, the prevalence of the disease in the study population, if in human subjects, the countries / regions considered, the demographics of participants, the setting, and any remaining inclusion / exclusion criteria considered. They then described the reference test or “gold standard,” if one was utilized.

Assignment

Reviewers described how the new and reference tests were assigned and any further details about the study design, for example whether the diagnostic test was biased towards sicker or healthier individuals or very clear-cut positive/negative cases.

Assessment

Reviewers described how the test was performed. For example, if provided, reviewers described the technical details of the assays used, when measurements were taken and by whom for both the standard and reference diagnostic tests. They then described how individuals were classified as positive or negative and whether there was evidence that the test results were precise or reproducible when repeated more than once. Reviewers described whether there was any missing data, whether some participants underwent only one test, or whether there were individuals with inconclusive results.

Results

Reviewers reported the estimated sensitivity, specificity, positive predictive value (PPV), and negative predicted value (NPV), as well as the confidence bounds around these measures, if provided.

Interpretation

Reviewers reported how well the test ruled in or rules out disease based on the population, if there were identified side effects, and patient adherence.

Extrapolation

Reviewers described how well this test will extrapolate outside the measured population.

Therapeutic Papers

Methods

Reviewers began by describing the study question(s) being investigated by the article. They then described the study population, the sample size, the prevalence of the disease in the study population, if in human subjects, the countries / regions considered, the demographics of participants, the setting, and any remaining inclusion / exclusion criteria considered.

Assignment

Reviewers described how the treatment is assigned, whether it was an interventional or observational study, whether randomization took place, etc.

Assessment

Outcome Assessment

Reviewers described the outcome that was assessed and evaluated whether it was appropriate given the underlying study question. They described whether there was any missing data, for example whether there were individuals lost to follow up. They then describe whether there were any potential sources of bias, for example lack of blinding in a randomized controlled trial.

Statistical Methods Assessment

Reviewers describe which statistical methods were used for inference and whether the methods were appropriate for the study. They then described whether adjustments were made for possible confounders.

Results

Reviewers described the estimated association between the treatment and outcome. They described measures of confidence or statistical significance, if provided.

Interpretation

Reviewers described whether a causal claim could be made. They described whether any side effects or interactions with other drugs were identified, as well as any subgroup findings.

Extrapolation

Reviewers describe how the study may extrapolate to a different species or population.

Collaborative Writing

Crowd-sourced writing with Manubot [[141](#)].

Additional Items

Competing Interests

Author	Competing Interests	Last Reviewed
Halie M. Rando	None	2020-03-22
Casey S. Greene	None	2020-03-22
Michael P. Robson	None	2020-03-23
Simina M. Boca	None	2020-03-23
Nils Wellhausen	None	2020-03-22
Ronan Lordan	None	2020-03-25
Christian Brueffer	None	2020-03-25
Sadipan Ray	None	2020-03-25
Lucy D'Agostino McGowan	None	2020-03-26
Anthony Gitter	None	2020-03-26
Anna Ada Dattoli	None	2020-03-26
Ryan Velazquez	None	2020-04-04
John P. Barton	None	2020-04-06
Jeffrey M. Field	None	2020-03-30

Author Contributions

Author	Contributions
Halie M. Rando	Project Administration, Writing - Original Draft, Writing - Review & Editing, Methodology
Casey S. Greene	Conceptualization, Software
Michael P. Robson	Software
Simina M. Boca	Methodology
Nils Wellhausen	Writing - Original Draft, Writing - Review & Editing
Ronan Lordan	Writing - Original Draft, Writing - Review & Editing
Christian Brueffer	Writing - Original Draft
Sadipan Ray	Writing - Original Draft
Lucy D'Agostino McGowan	Methodology, Writing - Original Draft
Anthony Gitter	Methodology
Anna Ada Dattoli	Writing - Original Draft
Ryan Velazquez	Methodology
John P. Barton	Writing - Original Draft, Writing - Review & Editing
Jeffrey M. Field	Writing - Original Draft

References

1.
Cramer
(2020-01-27) <https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200121-sitrep-1-2019-ncov.pdf>
2.
Ikejezie, Mr. Juniorcaius (WDC)
(2020-01-28) <https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200128-sitrep-8-ncov-cleared.pdf>
3.
Ikejezie, Mr. Juniorcaius (WDC)
(2020-03-11) <https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf>
4.
Ikejezie, Mr. Juniorcaius (WDC)
(2020-03-21) <https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200321-sitrep-61-covid-19.pdf>
5. **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://pubmed.ncbi.nlm.nih.gov/27344959/) · PMCID: [PMC7097822](https://pubmed.ncbi.nlm.nih.gov/PMC7097822/)
6. **Origin and evolution of pathogenic coronaviruses**
Jie Cui, Fang Li, Zheng-Li Shi
Nature Reviews Microbiology (2018-12-10) <https://doi.org/ggh4vb>
DOI: [10.1038/s41579-018-0118-9](https://doi.org/10.1038/s41579-018-0118-9) · PMID: [30531947](https://pubmed.ncbi.nlm.nih.gov/30531947/) · PMCID: [PMC7097006](https://pubmed.ncbi.nlm.nih.gov/PMC7097006/)
7. **The proximal origin of SARS-CoV-2**
Kristian G. Andersen, Andrew Rambaut, W. Ian Lipkin, Edward C. Holmes, Robert F. Garry
Nature Medicine (2020-03-17) <https://doi.org/ggn4dn>
DOI: [10.1038/s41591-020-0820-9](https://doi.org/10.1038/s41591-020-0820-9) · PMCID: [PMC7095063](https://pubmed.ncbi.nlm.nih.gov/PMC7095063/)
8. **A pneumonia outbreak associated with a new coronavirus of probable bat origin**
Peng Zhou, Xing-Lou Yang, Xian-Guang Wang, Ben Hu, Lei Zhang, Wei Zhang, Hao-Rui Si, Yan Zhu, Bei Li, Chao-Lin Huang, ... Zheng-Li Shi
Nature (2020-02-03) <https://doi.org/ggj5cg>
DOI: [10.1038/s41586-020-2012-7](https://doi.org/10.1038/s41586-020-2012-7) · PMID: [32015507](https://pubmed.ncbi.nlm.nih.gov/32015507/) · PMCID: [PMC7095418](https://pubmed.ncbi.nlm.nih.gov/PMC7095418/)
9. **Pangolin homology associated with 2019-nCoV**
Tao Zhang, Qunfu Wu, Zhigang Zhang
bioRxiv (2020-02-20) <https://doi.org/ggppvpt>
DOI: [10.1101/2020.02.19.950253](https://doi.org/10.1101/2020.02.19.950253)
10. **The concept of R_0 in epidemic theory**
J. A. P. Heesterbeek, K. Dietz
Statistica Neerlandica (1996-03) <https://doi.org/d29ch4>
DOI: [10.1111/j.1467-9574.1996.tb01482.x](https://doi.org/10.1111/j.1467-9574.1996.tb01482.x)

11. **Population Dynamics of Immune Responses to Persistent Viruses**
M. A. Nowak, C. R. M. Bangham
Science (1996-04-05) <https://doi.org/fggprd>
DOI: [10.1126/science.272.5258.74](https://doi.org/10.1126/science.272.5258.74) · PMID: [8600540](https://pubmed.ncbi.nlm.nih.gov/8600540/)

12. **Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study**
Joseph T Wu, Kathy Leung, Gabriel M Leung
The Lancet (2020-01) <https://doi.org/ggivr7>
DOI: [10.1016/s0140-6736\(20\)30260-9](https://doi.org/10.1016/s0140-6736(20)30260-9)

13. **The reproductive number of COVID-19 is higher compared to SARS coronavirus**
Ying Liu, Albert A Gayle, Annelies Wilder-Smith, Joacim Rocklöv
Journal of Travel Medicine (2020-02-13) <https://doi.org/ggnntv>
DOI: [10.1093/jtm/taaa021](https://doi.org/10.1093/jtm/taaa021) · PMID: [32052846](https://pubmed.ncbi.nlm.nih.gov/32052846/) · PMCID: [PMC7074654](https://pubmed.ncbi.nlm.nih.gov/PMC7074654/)

14. **Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2)**
Ruiyun Li, Sen Pei, Bin Chen, Yimeng Song, Tao Zhang, Wan Yang, Jeffrey Shaman
Science (2020-03-16) <https://doi.org/ggn6c2>
DOI: [10.1126/science.abb3221](https://doi.org/10.1126/science.abb3221) · PMID: [32179701](https://pubmed.ncbi.nlm.nih.gov/32179701/)

15. **Epidemiological parameters of coronavirus disease 2019: a pooled analysis of publicly reported individual data of 1155 cases from seven countries**
Shujuan Ma, Jiayue Zhang, Minyan Zeng, Qingping Yun, Wei Guo, Yixiang Zheng, Shi Zhao, Maggie H Wang, Zuyao Yang
medRxiv (2020-03-24) <https://doi.org/ggqhz3>
DOI: [10.1101/2020.03.21.20040329](https://doi.org/10.1101/2020.03.21.20040329)

16. **Early Transmissibility Assessment of a Novel Coronavirus in Wuhan, China**
Maimuna Majumder, Kenneth D. Mandl
SSRN Electronic Journal (2020) <https://doi.org/ggqhz3>
DOI: [10.2139/ssrn.3524675](https://doi.org/10.2139/ssrn.3524675)

17. **Time-varying transmission dynamics of Novel Coronavirus Pneumonia in China**
Tao Liu, Jianxiong Hu, Jianpeng Xiao, Guanhao He, Min Kang, Zuhua Rong, Lifeng Lin, Haojie Zhong, Qiong Huang, Aiping Deng, ... Wenjun Ma
bioRxiv (2020-02-13) <https://doi.org/dkx9>
DOI: [10.1101/2020.01.25.919787](https://doi.org/10.1101/2020.01.25.919787)

18. **Estimation of the reproductive number of novel coronavirus (COVID-19) and the probable outbreak size on the Diamond Princess cruise ship: A data-driven analysis**
Sheng Zhang, MengYuan Diao, Wenbo Yu, Lei Pei, Zhaofen Lin, Dechang Chen
International Journal of Infectious Diseases (2020-04) <https://doi.org/ggpx56>
DOI: [10.1016/j.ijid.2020.02.033](https://doi.org/10.1016/j.ijid.2020.02.033) · PMID: [32097725](https://pubmed.ncbi.nlm.nih.gov/32097725/) · PMCID: [PMC7110591](https://pubmed.ncbi.nlm.nih.gov/PMC7110591/)

19. **Estimation of the Transmission Risk of the 2019-nCoV and Its Implication for Public Health Interventions**
Tang, Wang, Li, Bragazzi, Tang, Xiao, Wu
Journal of Clinical Medicine (2020-02-07) <https://doi.org/ggmkf4>
DOI: [10.3390/jcm9020462](https://doi.org/10.3390/jcm9020462) · PMID: [32046137](https://pubmed.ncbi.nlm.nih.gov/32046137/) · PMCID: [PMC7074281](https://pubmed.ncbi.nlm.nih.gov/PMC7074281/)

20. <https://doi.org/10.1101/2020.01.27.20018952>

21. **Modelling the epidemic trend of the 2019 novel coronavirus outbreak in China**
Mingwang Shen, Zhihang Peng, Yanni Xiao, Lei Zhang
bioRxiv (2020-01-25) <https://doi.org/ggqhwz>
DOI: [10.1101/2020.01.23.916726](https://doi.org/10.1101/2020.01.23.916726)
22. **Novel coronavirus 2019-nCoV: early estimation of epidemiological parameters and epidemic predictions**
Jonathan M Read, Jessica RE Bridgen, Derek AT Cummings, Antonia Ho, Chris P Jewell
medRxiv (2020-01-28) <https://doi.org/dkzb>
DOI: [10.1101/2020.01.23.20018549](https://doi.org/10.1101/2020.01.23.20018549)
23. **Mechanistic-statistical SIR modelling for early estimation of the actual number of cases and mortality rate from COVID-19**
Lionel Roques, Etienne Klein, Julien Papaix, Samuel Soubeyrand
medRxiv (2020-03-24) <https://doi.org/ggqhz2>
DOI: [10.1101/2020.03.22.20040915](https://doi.org/10.1101/2020.03.22.20040915)
24. **Potential roles of social distancing in mitigating the spread of coronavirus disease 2019 (COVID-19) in South Korea**
Sang Woo Park, Kaiyuan Sun, Cécile Viboud, Bryan T Grenfell, Jonathan Dushoff
GitHub (2020) <https://github.com/parksw3/Korea-analysis/blob/master/v1/korea.pdf>
25. **Early dynamics of transmission and control of COVID-19: a mathematical modelling study**
Adam J Kucharski, Timothy W Russell, Charlie Diamond, Yang Liu, John Edmunds, Sebastian Funk, Rosalind M Eggo, Fiona Sun, Mark Jit, James D Munday, ... Stefan Flasche
The Lancet Infectious Diseases (2020-03) <https://doi.org/ggptcf>
DOI: [10.1016/s1473-3099\(20\)30144-4](https://doi.org/10.1016/s1473-3099(20)30144-4)
26. **Estimating the reproduction number of COVID-19 in Iran using epidemic modeling**
Ebrahim Sahafizadeh, Samaneh Sartoli
medRxiv (2020-03-29) <https://doi.org/ggqhxx>
DOI: [10.1101/2020.03.20.20038422](https://doi.org/10.1101/2020.03.20.20038422)
27. **Systems Approaches to Biology and Disease Enable Translational Systems Medicine**
Leroy Hood, Qiang Tian
Genomics, Proteomics & Bioinformatics (2012-08) <https://doi.org/f4f599>
DOI: [10.1016/j.gpb.2012.08.004](https://doi.org/10.1016/j.gpb.2012.08.004) · PMID: [23084773](https://pubmed.ncbi.nlm.nih.gov/23084773/) · PMCID: [PMC3844613](https://pubmed.ncbi.nlm.nih.gov/PMC3844613/)
28. **A systems approach to infectious disease**
Manon Eckhardt, Judd F. Hultquist, Robyn M. Kaake, Ruth Hüttenhain, Nevan J. Krogan
Nature Reviews Genetics (2020-02-14) <https://doi.org/ggnv63>
DOI: [10.1038/s41576-020-0212-5](https://doi.org/10.1038/s41576-020-0212-5) · PMID: [32060427](https://pubmed.ncbi.nlm.nih.gov/32060427/)
29. **Differential expression of serum/plasma proteins in various infectious diseases: Specific or nonspecific signatures**
Sandipan Ray, Sandip K. Patel, Vipin Kumar, Jagruti Damahe, Sanjeeva Srivastava
PROTEOMICS - Clinical Applications (2014-02) <https://doi.org/f2px3h>
DOI: [10.1002/prca.201300074](https://doi.org/10.1002/prca.201300074) · PMID: [24293340](https://pubmed.ncbi.nlm.nih.gov/24293340/)
30. **A new coronavirus associated with human respiratory disease in China**
Fan Wu, Su Zhao, Bin Yu, Yan-Mei Chen, Wen Wang, Zhi-Gang Song, Yi Hu, Zhao-Wu Tao, Jun-Hua Tian, Yuan-Yuan Pei, ... Yong-Zhen Zhang

Nature (2020-02-03) <https://doi.org/dk2w>

DOI: [10.1038/s41586-020-2008-3](https://doi.org/10.1038/s41586-020-2008-3) · PMID: [32015508](https://pubmed.ncbi.nlm.nih.gov/32015508/) · PMCID: [PMC7094943](https://pubmed.ncbi.nlm.nih.gov/PMC7094943/)

31. 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)

32. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation

Daniel Wrapp, Nianshuang Wang, Kizzmekia S. Corbett, Jory A. Goldsmith, Ching-Lin Hsieh, Olubukola Abiona, Barney S. Graham, Jason S. McLellan

Science (2020-02-19) <https://doi.org/ggmtk2>

DOI: [10.1126/science.abb2507](https://doi.org/10.1126/science.abb2507) · PMID: [32075877](https://pubmed.ncbi.nlm.nih.gov/32075877/)

33. SARS-CoV-2 infected host cell proteomics reveal potential therapy targets

Denisa Bojkova, Kevin Klann, Benjamin Koch, Marek Widera, David Krause, Sandra Ciesek, Jindrich Cinatl, Christian Münch

(2020-03-11) <https://doi.org/ggn4ds>

DOI: [10.21203/rs.3.rs-17218/v1](https://doi.org/10.21203/rs.3.rs-17218/v1)

34. 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 (2020-03) <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://pubmed.ncbi.nlm.nih.gov/32142651/) · PMCID: [PMC7102627](https://pubmed.ncbi.nlm.nih.gov/PMC7102627/)

35. 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

bioRxiv (2020-03-26) <https://doi.org/ggp7t4>

DOI: [10.1101/2020.03.21.990770](https://doi.org/10.1101/2020.03.21.990770)

36. Plasma proteome of severe acute respiratory syndrome analyzed by two-dimensional gel electrophoresis and mass spectrometry

J.-H. Chen, Y.-W. Chang, C.-W. Yao, T.-S. Chiueh, S.-C. Huang, K.-Y. Chien, A. Chen, F.-Y. Chang, C.-H. Wong, Y.-J. Chen

Proceedings of the National Academy of Sciences (2004-11-30) <https://doi.org/dtv8sx>

DOI: [10.1073/pnas.0407992101](https://doi.org/10.1073/pnas.0407992101) · PMID: [15572443](https://pubmed.ncbi.nlm.nih.gov/15572443/) · PMCID: [PMC535397](https://pubmed.ncbi.nlm.nih.gov/PMC535397/)

37. Analysis of multimerization of the SARS coronavirus nucleocapsid protein

Runtao He, Frederick Dobie, Melissa Ballantine, Andrew Leeson, Yan Li, Nathalie Bastien, Todd Cutts, Anton Andonov, Jingxin Cao, Timothy F. Booth, ... Xuguang Li

Biochemical and Biophysical Research Communications (2004-04) <https://doi.org/dbfwr9>

DOI: [10.1016/j.bbrc.2004.02.074](https://doi.org/10.1016/j.bbrc.2004.02.074) · PMID: [15020242](https://pubmed.ncbi.nlm.nih.gov/15020242/) · PMCID: [PMC7111152](https://pubmed.ncbi.nlm.nih.gov/PMC7111152/)

38. Nutraceuticals have potential for boosting the type 1 interferon response to RNA viruses including influenza and coronavirus

Mark F. McCarty, James J. DiNicolantonio

Progress in Cardiovascular Diseases (2020-02) <https://doi.org/ggpwx2>

DOI: [10.1016/j.pcad.2020.02.007](https://doi.org/10.1016/j.pcad.2020.02.007) · PMID: [32061635](https://pubmed.ncbi.nlm.nih.gov/32061635/)

39. **Reducing mortality from 2019-nCoV: host-directed therapies should be an option**
Alimuddin Zumla, David S Hui, Esam I Azhar, Ziad A Memish, Markus Maeurer
The Lancet (2020-02) <https://doi.org/ggkd3b>
DOI: [10.1016/s0140-6736\(20\)30305-6](https://doi.org/10.1016/s0140-6736(20)30305-6)
40. **Coronavirus Disease 2019 (COVID-19)**
CDC
Centers for Disease Control and Prevention (2020-02-11) <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>
41. **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)
42. **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/membr.05015-11](https://doi.org/10.1128/membr.05015-11) · PMID: [22390970](https://pubmed.ncbi.nlm.nih.gov/22390970/) · PMCID: [PMC3294426](https://pubmed.ncbi.nlm.nih.gov/PMC3294426/)
43. **Induction of cell cycle arrest and B cell terminal differentiation by CDK inhibitor p18(INK4c) and IL-6.**
L Morse, D Chen, D Franklin, Y Xiong, S Chen-Kiang
Immunity (1997-01) <https://www.ncbi.nlm.nih.gov/pubmed/9052836>
DOI: [10.1016/s1074-7613\(00\)80241-1](https://doi.org/10.1016/s1074-7613(00)80241-1) · PMID: [9052836](https://pubmed.ncbi.nlm.nih.gov/9052836/)
44. **The effects of hybridoma growth factor in conditioned media upon the growth, cloning, and antibody production of heterohybridoma cell lines.**
Y Zhu, B Jin, C Sun, C Huang, X Liu
Human antibodies and hybridomas (1993-01) <https://www.ncbi.nlm.nih.gov/pubmed/8431556>
PMID: [8431556](https://pubmed.ncbi.nlm.nih.gov/8431556/)
45. **Interleukin-6 is the central tumor growth factor in vitro and in vivo in multiple myeloma.**
B Klein, XG Zhang, M Jourdan, JM Boiron, M Portier, ZY Lu, J Wijdenes, J Brochier, R Bataille
European cytokine network <https://www.ncbi.nlm.nih.gov/pubmed/2104241>
PMID: [2104241](https://pubmed.ncbi.nlm.nih.gov/2104241/)
46. **The Biology and Medical Implications of Interleukin-6**
T. Tanaka, T. Kishimoto
Cancer Immunology Research (2014-04-03) <https://doi.org/f56dzb>
DOI: [10.1158/2326-6066.cir-14-0022](https://doi.org/10.1158/2326-6066.cir-14-0022) · PMID: [24764575](https://pubmed.ncbi.nlm.nih.gov/24764575/)
47. **Up-regulation of IL-6 and TNF- α induced by SARS-coronavirus spike protein in murine macrophages via NF- κ B pathway**
Wei Wang, Linbai Ye, Li Ye, Baozong Li, Bo Gao, Yingchun Zeng, Lingbao Kong, Xiaonan Fang, Hong Zheng, Zhenghui Wu, Yinglong She
Virus Research (2007-09) <https://doi.org/bm7m55>
DOI: [10.1016/j.virusres.2007.02.007](https://doi.org/10.1016/j.virusres.2007.02.007) · PMID: [17532082](https://pubmed.ncbi.nlm.nih.gov/17532082/) · PMCID: [PMC7114322](https://pubmed.ncbi.nlm.nih.gov/PMC7114322/)
48. **Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2⁺ cells in SARS patients: relation to the acute lung injury and pathogenesis of SARS**

L He, Y Ding, Q Zhang, X Che, Y He, H Shen, H Wang, Z Li, L Zhao, J Geng, ... S Jiang
The Journal of Pathology (2006-11) <https://doi.org/bwb8ns>
DOI: [10.1002/path.2067](https://doi.org/10.1002/path.2067) · PMID: [17031779](https://pubmed.ncbi.nlm.nih.gov/17031779/)

49. Cytokine Balance in the Lungs of Patients with Acute Respiratory Distress Syndrome

WILLIAM Y. PARK, RICHARD B. GOODMAN, KENNETH P. STEINBERG, JOHN T. RUZINSKI, FRANK RADELLA, DAVID R. PARK, JEROME PUGIN, SHAWN J. SKERRETT, LEONARD D. HUDSON, THOMAS R. MARTIN

American Journal of Respiratory and Critical Care Medicine (2001-11-15) <https://doi.org/ggqfq7>
DOI: [10.1164/ajrccm.164.10.2104013](https://doi.org/10.1164/ajrccm.164.10.2104013) · PMID: [11734443](https://pubmed.ncbi.nlm.nih.gov/11734443/)

50. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology

Rudragouda Channappanavar, Stanley Perlman

Seminars in Immunopathology (2017-05-02) <https://doi.org/ggqf2w>
DOI: [10.1007/s00281-017-0629-x](https://doi.org/10.1007/s00281-017-0629-x) · PMID: [28466096](https://pubmed.ncbi.nlm.nih.gov/28466096/) · PMCID: [PMC7079893](https://pubmed.ncbi.nlm.nih.gov/PMC7079893/)

51. 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://pubmed.ncbi.nlm.nih.gov/22595692/)

52. 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://pubmed.ncbi.nlm.nih.gov/8002928/) · PMCID: [PMC1138158](https://pubmed.ncbi.nlm.nih.gov/PMC1138158/)

53. 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://pubmed.ncbi.nlm.nih.gov/28066415/) · PMCID: [PMC5165036](https://pubmed.ncbi.nlm.nih.gov/PMC5165036/)

54. Interleukin-6; pathogenesis and treatment of autoimmune inflammatory diseases

Toshio Tanaka, Masashi Narazaki, Kazuya Masuda, Tadamitsu Kishimoto

Inflammation and Regeneration (2013) <https://doi.org/ggqmgf>
DOI: [10.2492/inflammregen.33.054](https://doi.org/10.2492/inflammregen.33.054)

55. Genentech Launches Phase III Trial of Actemra as Coronavirus Treatment

GEN - Genetic Engineering and Biotechnology News

(2020-03-19) <https://www.genengnews.com/virology/coronavirus/genentech-launches-phase-iii-trial-of-actemra-as-coronavirus-treatment/>

56. COVID-19 – Italy launches an independent trial on tocilizumab

COVID-19 – Italy launches an independent trial on tocilizumab | Univadis

<https://www.univadis.co.uk/viewarticle/covid-19-italy-launches-an-independent-trial-on-tocilizumab-715741>

57. 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://pubmed.ncbi.nlm.nih.gov/21865281/)

58. 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://pubmed.ncbi.nlm.nih.gov/28160426/)

59. Introduction to modern virology

N. J. Dimmock, A. J. Easton, K. N. Leppard
Blackwell Pub (2007)
ISBN: [9781405136457](https://www.isbn-international.org/product/9781405136457)

60. Coronaviruses

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://pubmed.ncbi.nlm.nih.gov/25870870/)

61. The potential chemical structure of anti-SARS-CoV-2 RNA-dependent RNA polymerase

Jrhuai 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 (2020-03-13) <https://doi.org/ggp6fm>
DOI: [10.1002/jmv.25761](https://doi.org/10.1002/jmv.25761) · PMID: [32167173](https://pubmed.ncbi.nlm.nih.gov/32167173/)

62. 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://pubmed.ncbi.nlm.nih.gov/23874596/) · PMCID: [PMC3707847](https://pubmed.ncbi.nlm.nih.gov/pmc/PMC3707847/)

63. Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model

Lisa Oestereich, Anja Lüdtke, Stephanie Wurr, Toni Rieger, César Muñoz-Fontela, Stephan Günther
Antiviral Research (2014-05) <https://doi.org/f524m3>
DOI: [10.1016/j.antiviral.2014.02.014](https://doi.org/10.1016/j.antiviral.2014.02.014) · PMID: [24583123](https://pubmed.ncbi.nlm.nih.gov/24583123/)

64. TEMPORARY REMOVAL: 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 (2020-03) <https://doi.org/ggpprd>
DOI: [10.1016/j.eng.2020.03.007](https://doi.org/10.1016/j.eng.2020.03.007)

65. 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://pubmed.ncbi.nlm.nih.gov/31774950/)

66. 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 Gotte
Journal of Biological Chemistry (2020-02-24) <https://doi.org/ggqm6x>
DOI: [10.1074/jbc.ac120.013056](https://doi.org/10.1074/jbc.ac120.013056) · PMID: [32094225](https://pubmed.ncbi.nlm.nih.gov/32094225/)

67. 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://pubmed.ncbi.nlm.nih.gov/29511076/) · PMCID: [PMC5844999](https://pubmed.ncbi.nlm.nih.gov/PMC5844999/)

68. 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://pubmed.ncbi.nlm.nih.gov/32020029/) · PMCID: [PMC7054408](https://pubmed.ncbi.nlm.nih.gov/PMC7054408/)

69. 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://pubmed.ncbi.nlm.nih.gov/28659436/) · PMCID: [PMC5567817](https://pubmed.ncbi.nlm.nih.gov/PMC5567817/)

70. 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)

71. 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, ... Jing Zhang
medRxiv (2020-03-12) <https://doi.org/ggqm6z>
DOI: [10.1101/2020.03.09.20032896](https://doi.org/10.1101/2020.03.09.20032896)

72. 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 (2020-01-31) <https://doi.org/ggjvr6>
DOI: [10.1056/nejmoa2001191](https://doi.org/10.1056/nejmoa2001191) · PMID: [32004427](https://pubmed.ncbi.nlm.nih.gov/32004427/) · PMCID: [PMC7092802](https://pubmed.ncbi.nlm.nih.gov/PMC7092802/)

73. Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment - Full Text View - ClinicalTrials.gov<https://clinicaltrials.gov/ct2/show/NCT04292730>

74. Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19) - Full Text View - ClinicalTrials.gov<https://clinicaltrials.gov/ct2/show/NCT04292899>

75. Adaptive COVID-19 Treatment Trial (ACTT) - Full Text View - ClinicalTrials.gov<https://clinicaltrials.gov/ct2/show/NCT04280705>

76. <https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-000936-23/FR>

77. **Mild/Moderate 2019-nCoV Remdesivir RCT - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04252664>
78. **Severe 2019-nCoV Remdesivir RCT - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04257656>
79. **Structural Design Principles for Delivery of Bioactive Components in Nutraceuticals and Functional Foods**
David Julian McClements, Eric Andrew Decker, Yeonhwa Park, Jochen Weiss
Critical Reviews in Food Science and Nutrition (2009-06-16) <https://doi.org/dt68m4>
DOI: [10.1080/10408390902841529](https://doi.org/10.1080/10408390902841529) · PMID: [19484636](https://pubmed.ncbi.nlm.nih.gov/19484636/)
80. **Nutraceutical therapies for atherosclerosis**
Joe W. E. Moss, Dipak P. Ramji
Nature Reviews Cardiology (2016-07-07) <https://doi.org/f9g389>
DOI: [10.1038/nrcardio.2016.103](https://doi.org/10.1038/nrcardio.2016.103) · PMID: [27383080](https://pubmed.ncbi.nlm.nih.gov/27383080/) · PMCID: [PMC5228762](https://pubmed.ncbi.nlm.nih.gov/PMC5228762/)
81. **Potential interventions for novel coronavirus in China: A systematic review**
Lei Zhang, Yunhui Liu
Journal of Medical Virology (2020-03-03) <https://doi.org/ggpx57>
DOI: [10.1002/jmv.25707](https://doi.org/10.1002/jmv.25707) · PMID: [32052466](https://pubmed.ncbi.nlm.nih.gov/32052466/)
82. **Phospholipids of Animal and Marine Origin: Structure, Function, and Anti-Inflammatory Properties**
Ronan Lordan, Alexandros Tsoupras, Ioannis Zabetakis
Molecules (2017-11-14) <https://doi.org/ggqmgg>
DOI: [10.3390/molecules22111964](https://doi.org/10.3390/molecules22111964) · PMID: [29135918](https://pubmed.ncbi.nlm.nih.gov/29135918/) · PMCID: [PMC6150200](https://pubmed.ncbi.nlm.nih.gov/PMC6150200/)
83. **Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology?**
Philip C. Calder
British Journal of Clinical Pharmacology (2013-03) <https://doi.org/ggqmgg>
DOI: [10.1111/j.1365-2125.2012.04374.x](https://doi.org/10.1111/j.1365-2125.2012.04374.x) · PMID: [22765297](https://pubmed.ncbi.nlm.nih.gov/22765297/) · PMCID: [PMC3575932](https://pubmed.ncbi.nlm.nih.gov/PMC3575932/)
84. **Proresolving Lipid Mediators and Mechanisms in the Resolution of Acute Inflammation**
Christopher D. Buckley, Derek W. Gilroy, Charles N. Serhan
Immunity (2014-03) <https://doi.org/f5wntr>
DOI: [10.1016/j.immuni.2014.02.009](https://doi.org/10.1016/j.immuni.2014.02.009) · PMID: [24656045](https://pubmed.ncbi.nlm.nih.gov/24656045/) · PMCID: [PMC4004957](https://pubmed.ncbi.nlm.nih.gov/PMC4004957/)
85. **Specialized pro-resolving mediators: endogenous regulators of infection and inflammation**
Maria C. Basil, Bruce D. Levy
Nature Reviews Immunology (2015-12-21) <https://doi.org/f9fgtd>
DOI: [10.1038/nri.2015.4](https://doi.org/10.1038/nri.2015.4) · PMID: [26688348](https://pubmed.ncbi.nlm.nih.gov/26688348/) · PMCID: [PMC5242505](https://pubmed.ncbi.nlm.nih.gov/PMC5242505/)
86. **The Lipid Mediator Protectin D1 Inhibits Influenza Virus Replication and Improves Severe Influenza**
Masayuki Morita, Keiji Kuba, Akihiko Ichikawa, Mizuho Nakayama, Jun Katahira, Ryo Iwamoto, Tokiko Watanebe, Saori Sakabe, Tomo Daidoji, Shota Nakamura, ... Yumiko Imai
Cell (2013-03) <https://doi.org/f4rbgb>
DOI: [10.1016/j.cell.2013.02.027](https://doi.org/10.1016/j.cell.2013.02.027) · PMID: [23477864](https://pubmed.ncbi.nlm.nih.gov/23477864/)
87. **Fish Oil-Fed Mice Have Impaired Resistance to Influenza Infection**
Nicole M. J. Schwerbrock, Erik A. Karlsson, Qing Shi, Patricia A. Sheridan, Melinda A. Beck

The Journal of Nutrition (2009-08) <https://doi.org/dv45f4>
DOI: [10.3945/jn.109.108027](https://doi.org/10.3945/jn.109.108027) · PMID: [19549756](https://pubmed.ncbi.nlm.nih.gov/19549756/) · PMCID: [PMC2709305](https://pubmed.ncbi.nlm.nih.gov/PMC2709305/)

88. Modulation of host defence against bacterial and viral infections by omega-3 polyunsaturated fatty acids

Marie-Odile Husson, Delphine Ley, Céline Portal, Madeleine Gottrand, Thomas Hueso, Jean-Luc Desseyn, Frédéric Gottrand
Journal of Infection (2016-12) <https://doi.org/f9pp2h>
DOI: [10.1016/j.jinf.2016.10.001](https://doi.org/10.1016/j.jinf.2016.10.001) · PMID: [27746159](https://pubmed.ncbi.nlm.nih.gov/27746159/)

89. Zinc and immunity: An essential interrelation

Maria Maares, Hajo Haase
Archives of Biochemistry and Biophysics (2016-12) <https://doi.org/f9c9b5>
DOI: [10.1016/j.abb.2016.03.022](https://doi.org/10.1016/j.abb.2016.03.022) · PMID: [27021581](https://pubmed.ncbi.nlm.nih.gov/27021581/)

90. Zinc-Dependent Suppression of TNF- α Production Is Mediated by Protein Kinase A-Induced Inhibition of Raf-1, I κ B Kinase β , and NF- κ B

Verena von Bülow, Svenja Dubben, Gabriela Engelhardt, Silke Hebel, Birgit Plümäkers, Holger Heine, Lothar Rink, Hajo Haase
The Journal of Immunology (2007-09-15) <https://doi.org/f3vs45>
DOI: [10.4049/jimmunol.179.6.4180](https://doi.org/10.4049/jimmunol.179.6.4180) · PMID: [17785857](https://pubmed.ncbi.nlm.nih.gov/17785857/)

91. Zinc activates NF- κ B in HUT-78 cells

Ananda S. Prasad, Bin Bao, Frances W. J. Beck, Fazlul H. Sarkar
Journal of Laboratory and Clinical Medicine (2001-10) <https://doi.org/cnc6fr>
DOI: [10.1067/mlc.2001.118108](https://doi.org/10.1067/mlc.2001.118108) · PMID: [11574819](https://pubmed.ncbi.nlm.nih.gov/11574819/)

92. Innate or Adaptive Immunity? The Example of Natural Killer Cells

E. Vivier, D. H. Raulet, A. Moretta, M. A. Caligiuri, L. Zitvogel, L. L. Lanier, W. M. Yokoyama, S. Ugolini
Science (2011-01-06) <https://doi.org/ckzg9g>
DOI: [10.1126/science.1198687](https://doi.org/10.1126/science.1198687) · PMID: [21212348](https://pubmed.ncbi.nlm.nih.gov/21212348/) · PMCID: [PMC3089969](https://pubmed.ncbi.nlm.nih.gov/PMC3089969/)

93. Zinc supplementation decreases incidence of infections in the elderly: effect of zinc on generation of cytokines and oxidative stress

Ananda S Prasad, Frances WJ Beck, Bin Bao, James T Fitzgerald, Diane C Snell, Joel D Steinberg, Lavoisier J Cardozo
The American Journal of Clinical Nutrition (2007-03) <https://doi.org/gggmgs>
DOI: [10.1093/ajcn/85.3.837](https://doi.org/10.1093/ajcn/85.3.837) · PMID: [17344507](https://pubmed.ncbi.nlm.nih.gov/17344507/)

94. The Role of Zinc in Antiviral Immunity

Scott A Read, Stephanie Obeid, Chantelle Ahlenstiel, Golo Ahlenstiel
Advances in Nutrition (2019-07) <https://doi.org/gggmgr>
DOI: [10.1093/advances/nmz013](https://doi.org/10.1093/advances/nmz013) · PMID: [31305906](https://pubmed.ncbi.nlm.nih.gov/31305906/) · PMCID: [PMC6628855](https://pubmed.ncbi.nlm.nih.gov/PMC6628855/)

95. Efficacy of Zinc Against Common Cold Viruses: An Overview

Darrell Hulisz
Journal of the American Pharmacists Association (2004-09) <https://doi.org/cf6pmt>
DOI: [10.1331/1544-3191.44.5.594.hulisz](https://doi.org/10.1331/1544-3191.44.5.594.hulisz) · PMID: [15496046](https://pubmed.ncbi.nlm.nih.gov/15496046/)

96. Zinc Lozenges May Shorten the Duration of Colds: A Systematic Review

Harri Harri
The Open Respiratory Medicine Journal (2011-06-23) <https://doi.org/bndmfq>
DOI: [10.2174/1874306401105010051](https://doi.org/10.2174/1874306401105010051) · PMID: [21769305](https://pubmed.ncbi.nlm.nih.gov/21769305/) · PMCID: [PMC3136969](https://pubmed.ncbi.nlm.nih.gov/PMC3136969/)

97. **Zn²⁺ Inhibits Coronavirus and Arterivirus RNA Polymerase Activity In Vitro and Zinc Ionophores Block the Replication of These Viruses in Cell Culture**
Aartjan J. W. te Velhuis, Sjoerd H. E. van den Worm, Amy C. Sims, Ralph S. Baric, Eric J. Snijder, Martijn J. van Hemert
PLoS Pathogens (2010-11-04) <https://doi.org/d95x4g>
DOI: [10.1371/journal.ppat.1001176](https://doi.org/10.1371/journal.ppat.1001176) · PMID: [21079686](https://pubmed.ncbi.nlm.nih.gov/21079686/) · PMCID: [PMC2973827](https://pubmed.ncbi.nlm.nih.gov/PMC2973827/)
98. **The SARS-coronavirus papain-like protease: Structure, function and inhibition by designed antiviral compounds**
Yahira M. Báez-Santos, Sarah E. St. John, Andrew D. Mesecar
Antiviral Research (2015-03) <https://doi.org/f63hjp>
DOI: [10.1016/j.antiviral.2014.12.015](https://doi.org/10.1016/j.antiviral.2014.12.015) · PMID: [25554382](https://pubmed.ncbi.nlm.nih.gov/25554382/) · PMCID: [PMC5896749](https://pubmed.ncbi.nlm.nih.gov/PMC5896749/)
99. **Vitamin B12 May Inhibit RNA-Dependent-RNA Polymerase Activity of nsp12 from the COVID-19 Virus**
Naveen Narayanan, Deepak T. Nair
(2020-03-22) <https://doi.org/ggqmqjc>
DOI: [10.20944/preprints202003.0347.v1](https://doi.org/10.20944/preprints202003.0347.v1)
100. **Vitamin C Mitigates Oxidative Stress and Tumor Necrosis Factor-Alpha in Severe Community-Acquired Pneumonia and LPS-Induced Macrophages**
Yuanyuan Chen, Guangyan Luo, Jiao Yuan, Yuanyuan Wang, Xiaoqiong Yang, Xiaoyun Wang, Guoping Li, Zhiguang Liu, Nanshan Zhong
Mediators of Inflammation (2014) <https://doi.org/f6nb5f>
DOI: [10.1155/2014/426740](https://doi.org/10.1155/2014/426740) · PMID: [25253919](https://pubmed.ncbi.nlm.nih.gov/25253919/) · PMCID: [PMC4165740](https://pubmed.ncbi.nlm.nih.gov/PMC4165740/)
101. **Intravenous infusion of ascorbic acid decreases serum histamine concentrations in patients with allergic and non-allergic diseases**
Alexander F. Hagel, Christian M. Layritz, Wolfgang H. Hagel, Hans-Jürgen Hagel, Edith Hagel, Wolfgang Dauth, Jürgen Kressel, Tanja Regnet, Andreas Rosenberg, Markus F. Neurath, ... Martin Raithel
Naunyn-Schmiedeberg's Archives of Pharmacology (2013-05-11) <https://doi.org/f48jsb>
DOI: [10.1007/s00210-013-0880-1](https://doi.org/10.1007/s00210-013-0880-1) · PMID: [23666445](https://pubmed.ncbi.nlm.nih.gov/23666445/)
102. **Vitamin C and Immune Function**
Anitra Carr, Silvia Maggini
Nutrients (2017-11-03) <https://doi.org/gfzrjs>
DOI: [10.3390/nu9111211](https://doi.org/10.3390/nu9111211) · PMID: [29099763](https://pubmed.ncbi.nlm.nih.gov/29099763/) · PMCID: [PMC5707683](https://pubmed.ncbi.nlm.nih.gov/PMC5707683/)
103. **Changes in Leucocyte Ascorbic Acid during the Common Cold**
R. Hume, Elspeth Weyers
Scottish Medical Journal (2016-06-25) <https://doi.org/ggqrfj>
DOI: [10.1177/003693307301800102](https://doi.org/10.1177/003693307301800102) · PMID: [4717661](https://pubmed.ncbi.nlm.nih.gov/4717661/)
104. **ASCORBIC ACID FUNCTION AND METABOLISM DURING COLDS**
C. W. M. Wilson
Annals of the New York Academy of Sciences (1975-09) <https://doi.org/bjfdtb>
DOI: [10.1111/j.1749-6632.1975.tb29312.x](https://doi.org/10.1111/j.1749-6632.1975.tb29312.x) · PMID: [1106304](https://pubmed.ncbi.nlm.nih.gov/1106304/)
105. **Vitamin C and Infections**
Harri Hemilä
Nutrients (2017-03-29) <https://doi.org/gfkb9n>
DOI: [10.3390/nu9040339](https://doi.org/10.3390/nu9040339) · PMID: [28353648](https://pubmed.ncbi.nlm.nih.gov/28353648/) · PMCID: [PMC5409678](https://pubmed.ncbi.nlm.nih.gov/PMC5409678/)

106. **Vitamin C and the common cold**
Harri Hemilä
British Journal of Nutrition (2007-03-09) <https://doi.org/fszhc6>
DOI: [10.1079/bjn19920004](https://doi.org/10.1079/bjn19920004) · PMID: [1547201](https://pubmed.ncbi.nlm.nih.gov/1547201/)
107. **Vitamin C for preventing and treating the common cold**
Harri Hemilä, Elizabeth Chalker
Cochrane Database of Systematic Reviews (2013-01-31) <https://doi.org/xz5>
DOI: [10.1002/14651858.cd000980.pub4](https://doi.org/10.1002/14651858.cd000980.pub4) · PMID: [23440782](https://pubmed.ncbi.nlm.nih.gov/23440782/)
108. **Vitamin C intake and susceptibility to pneumonia**
HARRI HEMILÄ
The Pediatric Infectious Disease Journal (1997-09) <https://doi.org/fkvs9d>
DOI: [10.1097/00006454-199709000-00003](https://doi.org/10.1097/00006454-199709000-00003) · PMID: [9306475](https://pubmed.ncbi.nlm.nih.gov/9306475/)
109. **Vitamin C Can Shorten the Length of Stay in the ICU: A Meta-Analysis**
Harri Hemilä, Elizabeth Chalker
Nutrients (2019-03-27) <https://doi.org/gfzscg>
DOI: [10.3390/nu11040708](https://doi.org/10.3390/nu11040708) · PMID: [30934660](https://pubmed.ncbi.nlm.nih.gov/30934660/) · PMCID: [PMC6521194](https://pubmed.ncbi.nlm.nih.gov/PMC6521194/)
110. **Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure**
Alpha A. Fowler, Jonathon D. Truwit, R. Duncan Hite, Peter E. Morris, Christine DeWilde, Anna Priday, Bernard Fisher, Leroy R. Thacker, Ramesh Natarajan, Donald F. Brophy, ... Matthew Halquist
JAMA (2019-10-01) <https://doi.org/ggqmh8>
DOI: [10.1001/jama.2019.11825](https://doi.org/10.1001/jama.2019.11825) · PMID: [31573637](https://pubmed.ncbi.nlm.nih.gov/31573637/) · PMCID: [PMC6777268](https://pubmed.ncbi.nlm.nih.gov/PMC6777268/)
111. **Vitamin D in the prevention of acute respiratory infection: Systematic review of clinical studies**
David A. Jolliffe, Christopher J. Griffiths, Adrian R. Martineau
The Journal of Steroid Biochemistry and Molecular Biology (2013-07) <https://doi.org/ggqmh9>
DOI: [10.1016/j.jsbmb.2012.11.017](https://doi.org/10.1016/j.jsbmb.2012.11.017) · PMID: [23220552](https://pubmed.ncbi.nlm.nih.gov/23220552/)
112. **Vitamin D: modulator of the immune system**
Femke Baeke, Tatiana Takiishi, Hannelie Korf, Conny Gysemans, Chantal Mathieu
Current Opinion in Pharmacology (2010-08) <https://doi.org/d43qtf>
DOI: [10.1016/j.coph.2010.04.001](https://doi.org/10.1016/j.coph.2010.04.001) · PMID: [20427238](https://pubmed.ncbi.nlm.nih.gov/20427238/)
113. **Evidence That Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths**
William B. Grant, Henry Lahore, Sharon L. McDonnell, Carole A. Baggerly, Christine B. French, Jennifer L. Aliano, Harjit Pal Bhattoa
(2020-03-30) <https://doi.org/ggqmjb>
DOI: [10.20944/preprints202003.0235.v2](https://doi.org/10.20944/preprints202003.0235.v2)
114. **Factors Affecting 25-Hydroxyvitamin D Concentration in Response to Vitamin D Supplementation**
Hajar Mazahery, Pamela von Hurst
Nutrients (2015-06-25) <https://doi.org/f7sztz>
DOI: [10.3390/nu7075111](https://doi.org/10.3390/nu7075111) · PMID: [26121531](https://pubmed.ncbi.nlm.nih.gov/26121531/) · PMCID: [PMC4516990](https://pubmed.ncbi.nlm.nih.gov/PMC4516990/)
115. **Optimal Nutritional Status for a Well-Functioning Immune System is an Important Factor to Protect Against Viral Infections**

Philip C. Calder, Anitra C. Carr, Adrian F. Gombart, Manfred Eggersdorfer
(2020-03-12) <https://www.preprints.org/manuscript/202003.0199/v1>

116. **The frontier between nutrition and pharma: The international regulatory framework of functional foods, food supplements and nutraceuticals**
Laura Domínguez Díaz, Virginia Fernández-Ruiz, Montaña Cámara
Critical Reviews in Food Science and Nutrition (2019-03-29) <https://doi.org/ggqs3w>
DOI: [10.1080/10408398.2019.1592107](https://doi.org/10.1080/10408398.2019.1592107) · PMID: [30924346](https://pubmed.ncbi.nlm.nih.gov/30924346/)
117. **Coronavirus Update: FDA and FTC Warn Seven Companies Selling Fraudulent Products that Claim to Treat or Prevent COVID-19**
Office of the Commissioner
FDA (2020-03-27) <https://www.fda.gov/news-events/press-announcements/coronavirus-update-fda-and-ftc-warn-seven-companies-selling-fraudulent-products-claim-treat-or>
118. **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://pubmed.ncbi.nlm.nih.gov/31894001/) · PMCID: [PMC6939334](https://pubmed.ncbi.nlm.nih.gov/PMC6939334/)
119. **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://pubmed.ncbi.nlm.nih.gov/23330954/)
120. **Neutralizing Monoclonal Antibodies as Promising Therapeutics against Middle East Respiratory Syndrome Coronavirus Infection**
Hui-Ju Han, Jian-Wei Liu, Hao Yu, Xue-Jie Yu
Viruses (2018-11-30) <https://doi.org/ggp87v>
DOI: [10.3390/v10120680](https://doi.org/10.3390/v10120680) · PMID: [30513619](https://pubmed.ncbi.nlm.nih.gov/30513619/) · PMCID: [PMC6315345](https://pubmed.ncbi.nlm.nih.gov/PMC6315345/)
121. **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://pubmed.ncbi.nlm.nih.gov/29230203/) · PMCID: [PMC5711820](https://pubmed.ncbi.nlm.nih.gov/PMC5711820/)
122. **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://pubmed.ncbi.nlm.nih.gov/28605249/) · PMCID: [PMC5612471](https://pubmed.ncbi.nlm.nih.gov/PMC5612471/)
123. **Neutralizing Antibodies in Patients with Severe Acute Respiratory Syndrome–Associated Coronavirus Infection**
Yuchun Nie, Guangwen Wang, Xuanling Shi, Hong Zhang, Yan Qiu, Zhongping He, Wei Wang, Gewei Lian, Xiaolei Yin, Liying Du, ... Mingxiao Ding
The Journal of Infectious Diseases (2004-09-15) <https://doi.org/cgqj5b>
DOI: [10.1086/423286](https://doi.org/10.1086/423286) · PMID: [15319862](https://pubmed.ncbi.nlm.nih.gov/15319862/)
124. **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://pubmed.ncbi.nlm.nih.gov/19216624/) · PMCID: [PMC2705284](https://pubmed.ncbi.nlm.nih.gov/PMC2705284/)

125. Prior Infection and Passive Transfer of Neutralizing Antibody Prevent Replication of Severe Acute Respiratory Syndrome Coronavirus in the Respiratory Tract of Mice

K. Subbarao, J. McAuliffe, L. Vogel, G. Fahle, S. Fischer, K. Tatti, M. Packard, W.-J. Shieh, S. Zaki, B. Murphy

Journal of Virology (2004-03-11) <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://pubmed.ncbi.nlm.nih.gov/15016880/) · PMCID: [PMC371090](https://pubmed.ncbi.nlm.nih.gov/PMC371090/)

126. 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://pubmed.ncbi.nlm.nih.gov/25030060/) · PMCID: [PMC4264590](https://pubmed.ncbi.nlm.nih.gov/PMC4264590/)

127. 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://pubmed.ncbi.nlm.nih.gov/24778221/) · PMCID: [PMC4024880](https://pubmed.ncbi.nlm.nih.gov/PMC4024880/)

128. 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/bqvpyh>

DOI: [10.1038/nature02145](https://doi.org/10.1038/nature02145) · PMID: [14647384](https://pubmed.ncbi.nlm.nih.gov/14647384/) · PMCID: [PMC7095016](https://pubmed.ncbi.nlm.nih.gov/PMC7095016/)

129. 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)

130. 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

bioRxiv (2020-03-12) <https://doi.org/ggnw4t>

DOI: [10.1101/2020.03.11.987958](https://doi.org/10.1101/2020.03.11.987958)

131. 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 Veasler

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://pubmed.ncbi.nlm.nih.gov/30712865/) · PMCID: [PMC6751136](https://pubmed.ncbi.nlm.nih.gov/PMC6751136/)

132. 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 (2017-12-15) <https://doi.org/ggqbpt>
DOI: [10.1128/jvi.01603-17](https://doi.org/10.1128/jvi.01603-17) · PMID: [29046448](https://pubmed.ncbi.nlm.nih.gov/29046448/) · PMCID: [PMC5709608](https://pubmed.ncbi.nlm.nih.gov/PMC5709608/)

133. 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://pubmed.ncbi.nlm.nih.gov/26098703/) · PMCID: [PMC5068219](https://pubmed.ncbi.nlm.nih.gov/PMC5068219/)

134. 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://pubmed.ncbi.nlm.nih.gov/21998254/) · PMCID: [PMC3280215](https://pubmed.ncbi.nlm.nih.gov/PMC3280215/)

135. 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://pubmed.ncbi.nlm.nih.gov/30792120/) · PMCID: [PMC6401214](https://pubmed.ncbi.nlm.nih.gov/PMC6401214/)

136. 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://pubmed.ncbi.nlm.nih.gov/29514901/) · PMCID: [PMC5923077](https://pubmed.ncbi.nlm.nih.gov/PMC5923077/)

137. 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://pubmed.ncbi.nlm.nih.gov/30830861/) · PMCID: [PMC6478436](https://pubmed.ncbi.nlm.nih.gov/PMC6478436/)

138. 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://pubmed.ncbi.nlm.nih.gov/15135736/)

139. 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-Rodríguez, 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://pubmed.ncbi.nlm.nih.gov/25093995/) · PMCID: [PMC4261026](https://pubmed.ncbi.nlm.nih.gov/PMC4261026/)

140. Using the MAARIE Framework To Read the Research Literature

M. Corcoran

American Journal of Occupational Therapy (2006-07-01) <https://doi.org/bqh97x>
DOI: [10.5014/ajot.60.4.367](https://doi.org/10.5014/ajot.60.4.367) · PMID: [16915865](https://pubmed.ncbi.nlm.nih.gov/16915865/)

141. **Open collaborative writing with Manubot**

Daniel S. Himmelstein, Vincent Rubinetti, David R. Slochower, Dongbo Hu, Venkat S. Malladi, Casey S. Greene, Anthony Gitter

PLOS Computational Biology (2019-06-24) <https://doi.org/c7np>

DOI: [10.1371/journal.pcbi.1007128](https://doi.org/10.1371/journal.pcbi.1007128) · PMID: [31233491](https://pubmed.ncbi.nlm.nih.gov/31233491/) · PMCID: [PMC6611653](https://pubmed.ncbi.nlm.nih.gov/PMC6611653/)