

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

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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. Short-term mitigation of viral impacts will require public health interventions, and long-term mitigation will require new diagnostics and therapeutics. The urgency of the pandemic has led to a rapidly emerging scientific literature on SARS-CoV-2 and COVID-19. This manuscript represents a collaborative effort to organize and consolidate this body of literature. We present information about the virus in the context of what is known about related viruses, describe the pathogenesis of COVID-19, and synthesize studies emerging about the diagnosis and treatment of COVID-19 alongside literature about related illnesses. We summarize and synthesize this emerging literature, with an eye towards discussing elements of the disease that will be fundamental to efforts to develop interventions. Our review is a collaboratively-authored, evolving document into which we seek to incorporate the ever-expanding body of information on the topic. This document provides a snapshot as of August, 2020. We continue to accept new contributions and anticipate future snapshots until technologies to mitigate the pandemic are widely deployed.

How to Contribute

We invite potential contributors to introduce themselves through GitHub:

<https://github.com/greenelab/covid19-review/issues/17>

We have established a community chat room on a service called Gitter: <https://gitter.im/covid19-review/community>.

More information about how to contribute is available in a README document on GitHub:

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

1 Introduction

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 describing 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 throughout China and subsequently around the world. At the time of the WHO's first situation report [1], 282 confirmed cases had been identified. Most of these cases were in China, but 1-2 exported cases had also been identified in each of several neighboring countries (Thailand, Japan, and the Republic of Korea). One week later, 4,593 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]. On April 4, 2020, the WHO reported that the global number of confirmed cases had surpassed one million [4]. 787,672 COVID-19 deaths had been reported worldwide as of August 19, 2020 (Figure 1).

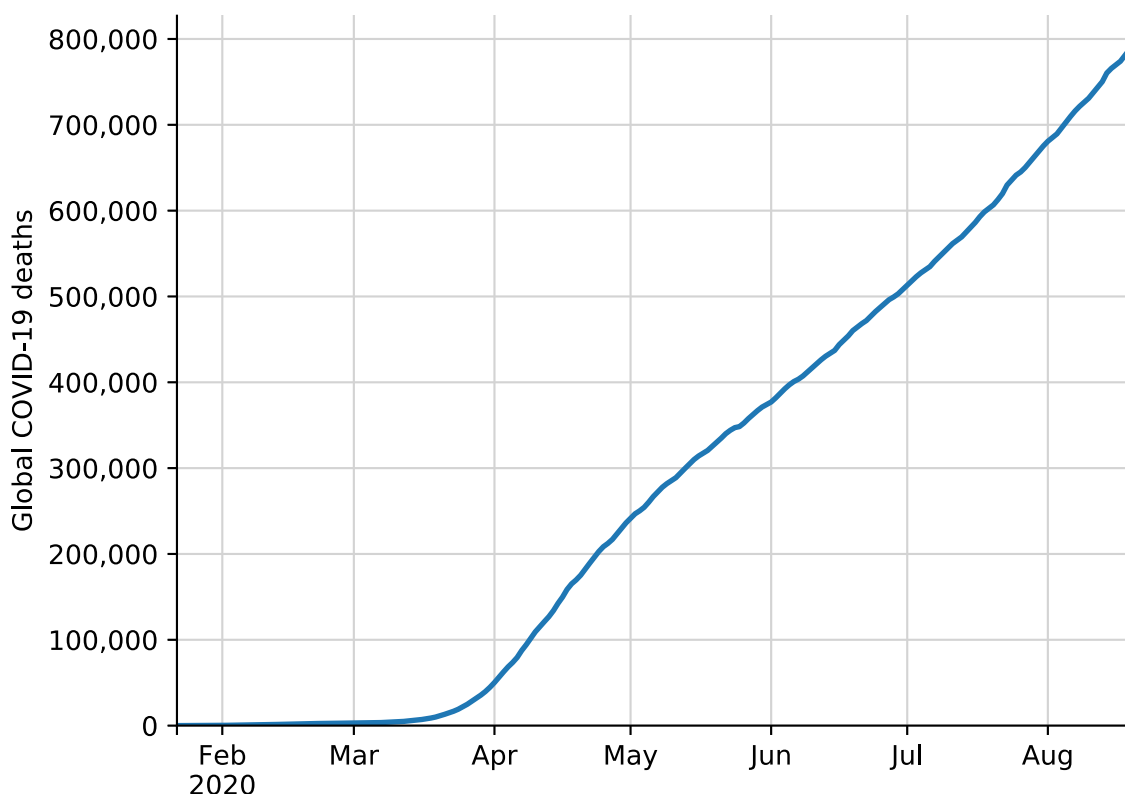


Figure 1: Cumulative global COVID-19 deaths since January 22, 2020. Data are from the COVID-19 Data Repository by the Center for Systems Science and Engineering at Johns Hopkins University [5].

Several review articles on aspects of COVID-19 have already been published. These have included reviews on the disease epidemiology [6], immunological response [7], diagnostics [8], and pharmacological treatments [7,9]. Others [10] and [11] provide narrative reviews of progress on some important ongoing COVID-19 research questions. However, research on these topics is proceeding so quickly that any static review is likely to quickly become dated. Our goal was to consolidate information about the virus in the context of related viruses and to synthesize rapidly emerging literature centered on the diagnosis and treatment of COVID-19. We developed infrastructure centered on the Manubot publishing system [12] to manage hundreds of contributions from the community to this living, scholarly document. We designed software to develop living figures like Figure 1, which automatically update using external data sources. Our primary goal is to sort and distill informative content out of the overwhelming flood of information [13] and help the broader

scientific community become more conversant this critical subject. Thus, our approach has been to develop a real-time, collaborative effort that welcomes submissions from scientists worldwide into this ongoing effort. This document represents the first snapshot, which aims to reflect the state of the field as of August, 2020. We plan to refine and expand this document until technologies to mitigate the pandemic are widely available.

1.1 Interdisciplinary Context

Collaboration across several broad areas of research is critical, as different areas provide different information and context necessary to understanding the virus and disease. This review provides a biological perspective on the SARS-CoV-2 virus and efforts to identify biomedical developments targeted at COVID-19. We provide only brief summaries of two other important perspectives on this pandemic: epidemiology and public health. Epidemiological analysis has investigated properties related to infection and transmission such as when infected individuals are contagious, how the virus is transmitted between individuals, the range of symptoms associated with infection and/or contagiousness in different individuals, and how rapidly the virus propagates between individuals, etc. Other areas of public health that address resource availability, inequity, human behavior, and other components that influence people's exposure to pathogens and ability to manage illness will also be critical to mounting a global response to the pandemic. Public health strategies to manage epidemics include anticipation and early detection of emerging diseases (aided by rapid development of diagnostics), containment (using strategies to test, trace and isolate such as widespread testing, contact tracing, quarantining and isolation), control and mitigation of spread (including social distancing), and elimination and eradication. An effective public health response requires response coordination, disease surveillance and intervention monitoring, risk communication and health education (including education about personal protective equipment and hand hygiene and containment of "infodemics" of false information), non-pharmaceutical measures to prevent and reduce transmission, and health interventions such as vaccines and other pharmaceuticals that can reduce transmission, curb morbidity and mortality, and mitigate the effects on health systems and other sectors of society [14]. These fields intersect with the topics addressed in this manuscript because they both inform and benefit from relevant biotechnological developments (e.g., accurate and fast diagnostic testing). However, the present analysis focuses less on human and social factors and more on the basic biology of infection, diagnosis, and recovery.

1.2 Rapid Characterization of SARS-CoV-2

Because the SARS-CoV-2 virus was not identified until COVID-19 was already a major health concern, scientists and physicians have used information about related viruses and diseases to guide both investigations of the biology of the virus and disease and the development of diagnostic, prophylactic, and therapeutic approaches. The first genome sequence of the SARS-CoV-2 virus was produced in January 2020 [cite]. Genomic analyses have made it possible to place the virus phylogenetically relative to coronaviruses infecting humans and other animals and to study diversity within the viral species. This rapid contextualization of the virus has made it possible to develop hypotheses rapidly about how the virus might infect cells, transmit between people, and respond to existing therapeutics. Understanding coronaviruses as a taxon and how humans respond to viral threats is foundational to understanding the pathogenesis of SARS-CoV-2 and the COVID-19 pandemic.

1.2.1 Origin and Evolution

A significant breakthrough in SARS-CoV-2 research was achieved through the successful full-length genome sequencing of the pathogen [15,16,17]. Multiple research groups have drafted the genome sequence of SARS-CoV-2 based on sequencing of clinical samples collected from bronchoalveolar lavage fluid (BALF) [15,17] or from BALF, throat swabs, or isolates of the virus cultured from BALF

[16]. SARS-CoV-2 had significant sequence homology with coronaviruses known to infect humans, with about 79% identity to SARS-CoV and 50% to MERS-CoV [16]. However, the highest degree of similarity was observed between SARS-CoV-2 and bat-derived SARS-like coronaviruses (bat-SL-CoVZC45 and bat-SL-CoVZXC21) [16,17]. The identity between SARS-CoV-2 and RATG13 is as high as 96.2% [17,18]. Nevertheless, some fragments between SARS-CoV-2 and RATG13 have a difference of up to 17%, suggesting a complex natural selection process during zoonotic transfer. While the S region is highly similar to that of viruses found in pangolins [19], there is no consensus about the origin of S in SARS-CoV-2. It could potentially be the result either of recombination or coevolution [18,20].

All the same, the evidence strongly supports a zoonotic origin of SARS-CoV-2. Though the intermediate host serving as the source for the zoonotic introduction of SARS-CoV-2 to human populations has not yet been identified, the SARS-CoV-2 virus has been placed within the coronavirus phylogeny through comparative genomic analyses. Genomic analyses and comparisons to other known coronaviruses suggest that SARS-CoV-2 is unlikely to have originated in a laboratory – either purposely engineered and released, or escaped – and instead evolved naturally in an animal host [21]. Regardless, while there is substantial support for the zoonotic origin of SARS-CoV-2, a lot remains unknown, causing issues regarding the SARS-CoV-2 evolutionary pattern [21].

Genetic variation in SARS-CoV-2 has been used to elucidate patterns over time and space. Numerous mutations [18,22,23] observed in individual SARS-CoV-2 genome sequences can be used to trace transmission patterns and have provided insight during outbreak investigations. Similar mutations observed in several patients may indicate that the patients belong to the same transmission group. The tracking of SARS-CoV-2 mutations is recognized as an essential tool for controlling outbreaks that may provide valuable insights into the paths of SARS-CoV-2's spread [24]. Several studies used phylogenetic analysis to determine the source of local COVID-19 outbreaks in Connecticut (USA), [25], the New York City area (USA) [26], and Iceland [27]. There is an ongoing effort to collect SARS-CoV-2 genomes throughout the COVID-19 outbreak, and as of August 7, 2020, more than 78,000 genome sequences have been collected from patients. The sequencing data can be found at GISAID [28], NCBI [29], and COVID-19 data portal [30].

1.2.2 Human Immune Response to Viral Threats

Understanding the fundamental organization of the human immune response to viral threats is critical to understanding the varied response to SARS-CoV-2. The human immune system utilizes a variety of innate and adaptive responses to protect against the pathogens it encounters. The innate immune system consists of barriers, such as the skin, mucous secretions, neutrophils, macrophages, and dendritic cells. It also includes cell-surface receptors that can recognize the molecular patterns of pathogens. The adaptive immune system utilizes antigen-specific receptors that are expressed on B and T lymphocytes. These components of the immune system typically act together; the innate response acts first, and the adaptive response begins to act several days after initial infection following the clonal expansion of T and B cells [31].

After a virus enters into a host cell, its antigen is presented by major histocompatibility complex 1 (MHC 1) molecules and is then recognized by cytotoxic T lymphocytes. One of the main immune responses that contribute to the onset of Acute Respiratory Distress Syndrome (ARDS) in COVID-19 patients is the cytokine storm, which causes an extreme inflammatory response due to a release of pro-inflammatory cytokines and chemokines by immune effector cells. In addition to respiratory distress, this mechanism can lead to organ failure and death in severe COVID-19 cases [32]. Research in response to prior outbreaks of hCoV-borne infections, such as SARS and MERS, have provided a strong foundation for hypotheses about the pathogenesis of SARS-CoV-2 as well as potential diagnostic and therapeutic approaches.

1.3 Role of the COVID-19 Review

With the worldwide scientific community uniting during 2020 to investigate SARS-CoV-2 and COVID-19 from a wide range of perspectives, findings from many disciplines are relevant on a rapid timescale to a broad scientific audience. Additionally, many findings are published as preprints, which are available prior to going through the peer review process. As a result, centralizing, summarizing, and critiquing new literature broadly relevant to COVID-19 can help to expedite the interdisciplinary scientific process that is currently happening at an advanced pace. We are particularly interested in providing background to the development of diagnostic, prophylactic, and therapeutic approaches to COVID-19. 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. The development of high-throughput, affordable methods for detecting active infections and sustained immunity will be critical to understanding and controlling the disease. The identification of interventions that can mitigate the effect of the virus on exposed and infected individuals is a significant research priority. Some possible approaches include the identification of existing pharmaceuticals that reduce the severity of infection, either by reducing the virus' virulence (e.g., antivirals) or managing the most severe symptoms of infection. Due to the long timeline for the development of novel pharmaceuticals, in most cases, research surrounding possible pharmaceutical interventions focuses on the identification and investigation of existing compounds whose mechanisms may be relevant to COVID-19. Other foci of current research include the identification of antibodies produced by survivors of COVID-19 and the development of vaccines. Understanding the mechanisms describing host-virus interactions between humans and SARS-CoV-2 is thus critical to identifying candidate therapeutics.

Thus, 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. We include information from both traditional peer-reviewed scientific literature and from preprints, which typically have not undergone peer review but have been critically evaluated by the scientists involved in this effort. The goal of this manuscript is to present preliminary findings within the broader context of COVID-19 research and to identify the broad interpretations of new research, as well as limitations to interpretability.

2 Virology

Examining the structure and basic functions of the SARS-CoV-2 virus is useful for understanding and predicting its pathogenesis and transmission. Genomic analysis of the virus provided early information about its phylogenetic position among other coronaviruses. These viruses are widely studied and their genomes are highly conserved, leading to strong hypotheses early on about how the structure and functions of the virus.

2.1 Coronaviruses

Coronaviruses (CoVs; order *Nidovirales*, family *Coronaviridae*, subfamily *Orthocoronavirinae*) are identified by their distinctive “crown-like” shape. These large viruses have spherical virions ranging from 100 to 160 nanometers (nm) in diameter. The virion is made up of a lipid envelope in which peplomers of 2-3 spike (S) glycoproteins are anchored, creating the crown [33, 34]. Coronaviruses are classified into four genera: alpha, beta, delta and gamma coronaviruses. Among them, alpha and beta coronaviruses infect mammalian species, gamma coronaviruses infect avian species and delta coronaviruses infect both mammalian and avian species [35]. The viruses were initially subdivided into these genera based on antigenic relationships of the spike (S), membrane (M), envelope (E), and

nucleocapsid (N) proteins but are now divided by phylogenetic clustering. Phylogenetic analysis of a PCR amplicon fragment from five patients along with the total virus genome of 29.8 Kb indicates that SARS-CoV-2 is a novel betacoronavirus belonging to the B lineage, also known as sarbecovirus, which also includes the human SARS coronavirus [36].

2.2 Genome Structure

All viruses in the *Nidovirales* order share fundamental characteristics: they are enveloped and non-segmented and have positive-sense (ssRNA+) genomes that contain many non-structural genes originating through ribosomal frameshifting [37]. Coronaviruses have some of the largest viral RNA genomes, ranging from 27 kilobases (Kb) to 32 Kb in length. The SARS-CoV-2 genome lies in the middle of this range at 29,903 bp [16]. Genome organization is highly conserved within the order [37]. A replicase gene comprises about two-thirds of the genome of coronaviruses. This polypeptide is translated into 16 non-structural proteins (nsp1-16, except in Gammacoronaviruses, where nsp1 is absent) that form replication machinery used to synthesize viral RNA [38]. The remaining third of the genome encodes structural proteins, including the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Additional accessory genes are sometimes present between these two regions, depending on the species or strain. Much attention has been focused on the S protein, which is a critical structure involved in cell entry. This structure has been visualized using cryo-electron microscopy [39].

2.3 Mechanisms of Cell Entry

In SARS-CoV, the most similar hCoV, the replication process is initiated by the viral spike protein: first, the virus binds to a host cell, and then the viral membrane fuses with the endosomal membrane to release the viral genome into the host cytoplasm. The coronavirus spike protein is structured in three segments: the ectodomain, a transmembrane anchor, and an intracellular tail [40]. The ectodomain contains two subdomains known as the S1 and S2 subunits, with the S1 (N-terminal) subunit guiding the binding of the virus to a host cell receptor and the S2 (C-terminal) subunit guiding the fusion process [40]. The ectodomain forms the crown-like structures on the viral membrane, with the S1 domain forming the head of the crown and containing the Receptor Binding Motif (RBM) that binds a host receptor, while the S2 domain forms the stalk that supports the head [41]. Coronaviruses bind to a range of host receptors [42,43], with binding conserved only at the genus level [35]. Betacoronaviruses are known to bind to CEACAM1, Neu 5,9 Ac2, and Angiotensin-Converting Enzyme 2 (ACE2) [42]. Similar to SARS-CoV, SARS-CoV-2 exhibits redundancy in which host proteases it can use to cleave the S protein [44]. Specifically, both transmembrane protease serine protease-2 (TMPRSS2) and cathepsins B/L have been shown to mediate SARS-CoV-2 S protein proteolytic priming, and small molecule inhibition of these enzymes fully inhibited viral entry *in vitro* [44,45].

After the virus binds to a host cell receptor, the viral and plasma membranes must then fuse. Many coronaviruses are cleaved at the S1-S2 boundary and remain non-covalently bound until fusion to the host cell is achieved, with the S1 subunit stabilizing the S2 subunit during the membrane fusion process [46]. This priming of the S protein is induced by the binding of cellular proteases [47,48]. A second cleavage site within S2 is thought to activate S for fusion by inducing conformational change [46]. Electron microscopy suggests that in some coronaviruses, including SARS-CoV and MERS-CoV, a six-helix bundle separates the two subunits in the postfusion conformation, and the unusual length of this bundle facilitates membrane fusion through the release of additional energy [35]. However, research in SARS-CoV suggests that, in addition to fusion with the plasma membrane, viruses may also be taken up by cells through endocytosis [49]. Once the virus enters a host cell, the replicase gene is translated and assembled into the viral replicase complex, which can synthesize dsRNA genome from the genomic ssRNA(+). Finally, the dsRNA genome is transcribed and replicated to create viral mRNAs and new ssRNA(+) genomes [37,50].

2.4 Host-CoV Dynamics

Most coronaviruses are considered zoonotic viruses with little to no transmission observed in humans. However, coronaviruses include human coronavirus (HCoV) strains associated with multiple respiratory diseases of varying severity, ranging from common cold to severe pneumonia, with severe symptoms mostly observed in immunocompromised individuals [51]. Approximately one-third of common cold infections in humans is attributable to four out of six previously known human coronaviruses (HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1) that are globally circulating in the human population [52, 53]. In the past two decades, however, highly pathogenic human coronaviruses have been identified, including the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and the Middle East respiratory syndrome coronavirus (MERS-CoV) although both infections were largely confined to specific geographic regions [52, 54, 55].

2.5 Evolution and Virulence

Comparative genomic analysis reveals that several regions of the coronavirus genome are likely critical to virulence. The S1 domain of the spike protein, which contains the RBM, evolves more rapidly than S's S2 domain [42, 43]. However, even within the S1 domain, some regions are more conserved than others, with the receptors in S1's N-terminal domain (S1-NTD) evolving more rapidly than those in its C-terminal domain (S1-CTD) [43]. Both S1-NTD and S1-CTD are involved in receptor binding and can function as receptor binding domains (RBDs) to bind proteins and sugars [42], but RBDs in the S1-NTD typically bind to sugars, while those in the S1-CTD recognize protein receptors [35]. Viral receptors show higher affinity with protein receptors than sugar receptors [35], which suggests that positive selection on or relaxed conservation of the S1-NTD preferentially might reduce the risk of a deleterious mutation that would prevent binding. The SARS-CoV-2 S protein also contains a RRAR furin recognition site at the S1/S2 junction [39, 46], setting it apart from bat coronavirus RaTG13, with which it shares 96% genome sequence identity, and SARS-CoV [17]. Such furin cleavage sites are commonly found in highly virulent influenza viruses, and as such may contribute to the heightened pathogenicity of SARS-CoV-2 [56, 57]. Cell entry by the virus is a critical component to pathogenesis and therefore an important process to understand when examining possible therapeutics.

Evolution in SARS-CoV-2 has also been observed over a short timescale. After zoonotic transfer, SARS-CoV-2 continued evolving in the human population [22]. The SARS-CoV-2 mutation rate is moderate compared to other RNA viruses [23], and that restricts SARS-CoV-2 evolution pace. Nevertheless, genomic data show some significant statistical evidence of ongoing evolution. There are two known variants of the spike protein that differ by a single amino acid at position 614 (G614 and D614), and there is evidence that G614 has already become dominant over D614 by June 2020 [58]. While there is a hypothesis that this genomic change increased the SARS-CoV-2 infectivity and virulence, there is no data yet to support or discard this hypothesis reliably [59]. One study [23] has reported more than 198 recurrent mutations using a dataset of 7666 curated sequences showing the dynamic of SARS-CoV-2 evolution. Much uncertainty remains about SARS-CoV-2's evolutionary trends though it is evident that SARS-CoV-2 exhibits moderate potential for further evolution.

3 Pathogenesis

Pathogenesis is made up of three major components: entry, replication, and spread [60]. The basic mechanisms of cell entry are known to be similar among coronaviruses and are discussed above. hCoV are not common, but combining existing research in SARS-CoV and new research in SARS-CoV-2 led to early hypotheses about how the SARS-CoV-2 virus was likely to infect human cells. These insights led to predictions about which tissues, organs, and systems would be most susceptible to SARS-CoV-2 infection. The current pandemic of COVID-19, caused by the severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2), represents an acute global health crisis with symptoms for reported cases ranging from mild to severe or fatal [61] and including outcomes such as acute respiratory distress, acute lung injury and other pulmonary complications.

3.1 Cell Susceptibility

ACE2 and Transmembrane Serine Protease 2 (TMPRSS2) have been identified as a prime receptor and a critical protease, respectively, facilitating SARS-CoV/CoV-2 entry into a target cell [39,44,62,63,64]. This finding has led to a hypothesized role for ACE2 and TMPRSS2 expression in determining which cells, tissues and organs are most likely to be infected by SARS-CoV-2. The ACE2 receptor is expressed in numerous organs, such as the heart, kidney, and intestine, but most prominently in alveolar epithelial cells, which is expected to contribute to the virus' association with lung pathology [65,66]. Clinical investigations of COVID-19 patients have detected SARS-CoV-2 transcripts in bronchoalveolar lavage fluid (93% of specimens), sputum (72%), nasal swabs (63%), fibrobronchoscopy brush biopsies (46%), pharyngeal swabs (32%), feces (29%) and blood (1%) [67]. Two studies reported that SARS-CoV-2 could not be detected in the urine specimens [67,68]; however, a third study identified four urine samples (out of 58) that were positive for SARS-CoV-2 nucleic acids [69]. Respiratory failure remains the leading cause of death for COVID-19 patients [70]. Besides major pulmonary damage, SARS-CoV-2 infection can damage many other organ systems including the heart [71], kidney [72,73], liver [74], and gastrointestinal tract [75,76]. As it becomes clearer that SARS-CoV-2 infection can damage multiple organs, the scientific community is pursuing multiple avenues of investigation in order to build a consensus about how the virus affects the human body.

To quickly associate the clinical outcomes with SARS-CoV-2 infection, researchers are taking advantage of “omics” technologies to profile the expression of coronavirus entry factors across the tissues. Viral progression may be enhanced by active upregulation of ACE2 on cell surfaces following or during a response to infection. In several preliminary assays and an analysis of previous microarray data, Wang et al. reported that ACE2 is significantly upregulated following infection by other coronaviruses, including SARS-CoV and MERS-CoV, as well as viruses such as rhinovirus and influenza virus [65]. Additionally, direct stimulation with inflammatory cytokines such as type I interferons resulted in the upregulation of ACE2, with treated groups showing 4-fold higher ACE2 expression than control groups at 18 hours post-treatment [65]. Though whether SARS-CoV-2 infection facilitates positive regulation of its own transmission between host cells is still unclear, the host immune response itself likely plays a key role in mediating infection-associated pathologies. One severe example includes reports of cytokine storm-like responses in patients with particularly severe infections, in which the overproduction of inflammatory cytokines leads to systemic inflammation and potentially multi-organ failure, which may very well accelerate the spread of virus in the host [65,77]. [78] describe the concept of the cytokine storm in detail, although [79] claim that the widespread use of the term can be misleading.

3.2 Virulence of SARS-CoV-2 in Humans

Like that of SARS-CoV, SARS-CoV-2 entry into host cells is mediated by the interaction between the viral spike glycoprotein (S) and human angiotensin-converting enzyme 2 (ACE2) [44,46,80,81,82,83,84,85]. Differences between the two viruses in their interactions between the S protein and hACE2 may also partially account for the increased transmissibility seen in the current COVID-19 pandemic. Recent studies have reported conflicting binding constants for the S protein-hACE2 interaction, though they agree that SARS-CoV-2 S protein binds with equal if not greater affinity than does SARS-CoV S protein [39,46,83]. The C-terminal domain of the SARS-CoV-2 S protein in particular was identified as the key region of the virus that interacts with the human ACE2 (hACE2) receptor, and the crystal structure of the C-terminal domain of SARS-CoV-2 S protein in complex with human ACE2 reveals stronger interaction and higher affinity for receptor binding than SARS-CoV [84].

Among the 14 key binding residues identified in the SARS-CoV S protein, 8 are conserved in SARS-CoV-2 and the remaining 6 are semi-conservatively substituted, potentially explaining variation in binding affinity [46,83]. Recent crystal structures have shown that the receptor-binding domain (RBD) of SARS-CoV-2 S protein, like that of other coronaviruses, undergoes stochastic hinge-like movement that flips it from a “closed” conformation, in which key binding residues are hidden at the interface between protomers, to an “open” one [39,46]. Because the RBD plays such a critical role in viral entry, blocking its interaction with ACE2 represents a promising therapeutic approach. Nevertheless, despite the high structural homology between SARS-CoV-2 RBD and that from SARS-CoV, monoclonal antibodies targeting SARS-CoV-RBD failed to bind SARS-CoV-2-RBD [39]. Promisingly though, sera from convalescent SARS patients inhibited SARS-CoV-2 viral entry *in vitro*, albeit with lower efficiency than it inhibited SARS-CoV [44].

3.3 Immune Response to SARS-CoV-2

Pathogens have developed ways to evade the immune system as well as various ways to manipulate the host immunity.

Disease symptoms can be caused by a pathogen or by the reaction of the immune system to the pathogen. The host immune system can defend against infection but can also sometimes cause too much damage to the host [86,87]. There is a review on interferon-mediated innate antiviral responses initiated by the virus-infected cells themselves, which can sometimes have inflammatory and other systemic effects [88]. Also, there is a review on the innate immune system response with a focus on innate immune cells and responses other than the interferon-mediated responses; the review also approaches the question of how the innate immune response can confer protection or induce pathogenesis through a dysregulated response [89]. There are also acquired immunity responses to SARS-CoV-2. There is a review on the levels of different SARS-CoV-2-specific antibodies detected over the course of an infection [90]. A review of T-cell mediated responses to respiratory coronaviruses notes a large reduction in T-cells associated with the acute phase of SARS (from SARS-CoV-1) [91]. So far, some articles and reviews on SARS-CoV-2 mention evidence for reduction in the number of CD4 and CD19 T-cells as well as NK-cells [89,92]. As a brief immunology background primer for vaccines, which we discuss later, we note that adaptive immunity also has mechanisms for long-term immunity: during a first exposure to a pathogen innate and also later acquired immune responses operate; at the same time, the acquired immune system forms memory B cells and memory T cells based on this experience so that on a possible future second exposure to the same pathogen an earlier/faster and stronger acquired immune response is generated which largely prevents or greatly reduces infection. Vaccines are in general attenuated or inactivated pathogens or antigen parts of pathogens which are meant to generate long-term memory of a pathogen so that if a person is exposed to the same pathogen in the future they will have a strong immunity memory response; we will describe specific research into vaccines in detail later. Other immune system features and pathogen-immune system interactions which are related to particular diagnostics and therapeutics are described within the Diagnostics and Therapeutics sections.

3.3.1 Cytokine Storm

In progress 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 [93], 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 [94]. 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 [95]. 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 heavy damage of the endothelium of blood vessels, which disrupts the balance between the pro- and anti-inflammatory response [95]. 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 in ARDS and Severe Acute Respiratory Syndrome (SARS) [96], also caused by the new coronavirus. One severe example includes reports of cytokine storm-like responses in patients with particularly severe infections, in which the overproduction of inflammatory cytokines leads to systemic inflammation and potentially multi-organ failure, which may very well accelerate the spread of virus in the host [65,77]. [78] describe the concept of the cytokine storm in detail, although [79] claim that the widespread use of the term can be misleading. ->

3.4 Clinical Presentation of COVID-19

A great diversity of symptom profiles has been observed for COVID-19, although a large study from Wuhan, China suggests fever and cough as the two most common symptoms on admission [97]. One early retrospective study in China described the clinical presentations of patients infected with SARS-CoV-2 as including lower respiratory tract infection with fever, dry cough, and dyspnea [98]. This study [98] noted that upper respiratory tract symptoms were less common, which suggests that the virus targets cells located in the lower respiratory tract. However, data from the New York City region [99,100] showed variable rates of fever as a presenting symptom, suggesting that symptoms may not be consistent across samples. These differences are present when comparing both between institutions in similar locations and between different regions experiencing COVID-19 outbreaks, leading to conflicting reports of the frequency of fever as a presenting symptom for patients upon hospital admission. For example, even within New York City, one study [99] identified low oxygen saturation (<90% without the use of supplemental oxygen or ventilation support) in a significant percentage of patients on presentation, while another study [100] reported cough, fever, and dyspnea as the most common presenting symptoms.

Patients may also experience loss of smell, myalgias (muscle aches), fatigue, or headache.

The variability of both which symptoms present and their severity makes it difficult for public health agencies to provide clear recommendations for citizens regarding what symptoms indicate SARS-CoV-2 infection and should prompt isolation.

For example, accumulating evidence suggests that gastrointestinal symptoms presentations occur [101]. The CDC has updated its list of symptoms suggestive of COVID-19 to include nausea and vomiting, as well congestion and runny nose [61]. A recent preprint using data from an app-based survey of 500,000 individuals in the US found that among those tested for SARS-CoV-2, a loss of taste or smell, fever, and a cough were significant predictors of a positive test result [102]. It is important to note that in this study, the predictive value of symptoms may be underestimated if they are not specific to COVID-19 because the outcome measured was a positive, as opposed to a negative, COVID-19 test result. At the time the surveys were conducted, due to limits in US testing infrastructure, respondents typically needed to have some symptoms known to be specific to COVID-19 in order to qualify for testing in the first place.

The significant range of individual outcomes observed has led to interest in which factors influence disease severity. The reported hospitalization rates have been wide-ranging and appear to be influenced by age and location, with several underlying health conditions being disproportionately reported among hospitalized patients [103]. Among patients who are admitted to the hospital, outcomes have generally been poor, with rates of admission to the intensive care unit (ICU) upwards of 15% in both Wuhan, China and Italy [97,104,105]. Several studies have also investigated which factors are likely to influence COVID-19 outcomes. For example, a Chinese retrospective study [98]

found that a higher probability of mortality was associated with older age and higher Sequential Organ Failure Assessment scores, as well as high levels of d-dimer. Mortality might be associated with other biomarkers measured in blood samples including lactate dehydrogenase and cardiac troponin I, although these analyses may not have been appropriately corrected for multiple testing. Zhou et al. [98] reported that survivors continued to have detectable viral nucleic acids in respiratory specimens for a median of 20 days and a maximum of at least 37 days. A later study reported radiographic findings such as ground-glass opacity and bilateral patchy shadowing in the lungs of many hospitalized patients, and most COVID-19 patients had lymphocytopenia, meaning they had low levels of lymphocytes (a type of white blood cell) [97].

COVID-19 can affect diverse body systems in addition to causing respiratory problems [106]. For example, COVID-19 can lead to acute kidney injury, especially in patients with severe respiratory symptoms or certain preexisting conditions [107]. It can also cause neurological complications [108,109], potentially including stroke, seizures or meningitis [110,111].

COVID-19 has also been associated with an increased incidence of large vessel stroke, particularly in patients under the age of 40 [112], and other thrombotic events including pulmonary embolism and deep vein thrombosis [113]. The mechanism behind these complications has been suggested to be related to coagulopathy with reports of antiphospholipid antibodies present [114] and elevated levels of d-dimer and fibrinogen degradation products (FDP) elevated in deceased patients [115]. Other viral infections have been associated with coagulation defects; notably SARS was also found to lead to disseminated intravascular coagulation (DIC) and was associated with both pulmonary embolism and deep vein thrombosis [116]. A wide range of viral infections can affect the coagulation cascade. The mechanism behind these insults has been suggested to be related to inflammation-induced increases in the von Willebrand factor (VWF) clotting protein, leading to a pro-coagulative state [116]. Abnormal clotting (thromboinflammation or coagulopathy) has been increasingly discussed recently as a possible key mechanism in many cases of severe COVID-19, and may be associated with the high d-dimer levels often observed in severe cases [117,118,119]. This excessive clotting in lung capillaries has been suggested to be related to a dysregulated activation of the complement system, part of the innate immune system [120,121].

The presentation of COVID-19 infection can vary greatly among pediatric patients and in some cases manifests in distinct ways from COVID-19 in adults. [122] reviewed 17 studies on children infected with COVID-19 during the early months of the COVID-19 epidemic in China and one study from Singapore. Of the more than a thousand cases described, the most commonly reports were for mild symptoms such as fever, dry cough, fatigue, nasal congestion and/or runny nose, while three children were reported to be asymptomatic. Severe lower respiratory infection was described in only one of the pediatric cases reviewed. Gastrointestinal symptoms such as vomiting or diarrhea were occasionally reported. Radiologic findings were not always reported in the case studies reviewed by [122], but when they were mentioned they included bronchial thickening, ground-glass opacities, and/or inflammatory lesions. Neurological symptoms have also been reported [123].

These analyses indicate that generally, most pediatric cases of COVID-19 are not severe. However, serious complications and, in rare cases, death have occurred [124]. Of particular interest, children have occasionally experienced a serious inflammatory syndrome, multisystem inflammatory syndrome in children (MIS-C), after COVID-19 infection. This syndrome is similar in some respects to Kawasaki disease or to Kawasaki disease shock syndrome [125,126,127] and is thought to be a distinct clinical manifestation of SARS-CoV-2 due to its distinct cytokine profile and the presence of burr cells in peripheral blood smears [128]. MIS-C has been associated with heart failure in some cases [129]. [130] reported a single case of an adult who appeared to show symptoms similar to MIS-C after exposure to COVID-19, but cautioned against broad conclusions; [131] reported another such possible adult case.

3.5 Systems Approaches to 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 [132]. 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 [133]. Omics-based studies also provided meaningful information regarding host immune responses and surrogate protein markers in several viral, bacterial and protozoan infections [134]. The complex pathogenesis and clinical manifestations of SARS-CoV-2 infection are not understood adequately yet. 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.

3.5.1 Proteomics

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. 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 [135]. 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 [44]. However, despite the high level of sequence homology, certain protein structures might be immunologically distinct, prohibiting effective cross-neutralization across different SARS strains [136]. Consequently, earlier proteome-level studies on SARS-CoV can also provide some essential information regarding the new pathogen [137,138]. 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. Using such databases, the systems level reconstruction of the PPI (Protein-Protein Interaction) enabled the generation of hypotheses on the mechanism of action of SARS-CoV-2 and suggested drug targets. In an initial study [139], 26 of the 29 SARS-CoV-2 proteins were cloned and expressed in HEK293T kidney cells, allowing for the identification of 332 high-confidence human proteins that interact with them. Notably, this study suggested that SARS-CoV-2 interacts with innate immunity pathways. The ranking of pathogens with respect to their interactome's similarity to SARS-CoV-2 suggested *West Nile Virus*, *Mycobacterium tuberculosis*, and *Human papillomavirus* as the top three hits. However, given the lung symptoms associated with COVID-19, the *Mycobacterium tuberculosis* host-pathogen interactome could also provide new insights to the mechanism of SARS-CoV-2 infection. In addition, it was suggested that the envelope protein E could disrupt the host bromodomain-containing proteins, i.e., BRD2 and BRD4, binding to histone. The Spike protein S could likely intervene in the virus fusion through modulating the GOLGA7-ZDHHC5 acyl-transferase complex to increase palmitoylation.

Another study [140], used patient-derived peripheral blood mononuclear cells (PBMCs) to identify 251 host proteins targeted by SARS-CoV-2 and the disruption of more than 200 host proteins following the infection. The network analysis showed in particular that non-structural proteins 9 and 10 (nsp9 and nsp10) interacted with NFKB1 that usually represses NF- κ B. This finding could explain the exacerbation of the immune response that shape the pathology and the high cytokine levels possibly due to the chemotaxis of neutrophils mediated by IL-8 and IL-6. Finally, it was suggested [141] that protein E of both SARS-CoV and SARS-CoV-2 has a conserved Bcl-2 Homology 3 (BH3)-like motif, that could inhibit anti-apoptosis proteins BCL2 and trigger the apoptosis of T cells. Several known compounds were

suggested to disrupt the host-pathogen protein interactome were suggested mostly through the inhibition of host proteins.

3.5.2 Transcriptomics

To quickly associate the clinical outcomes with SARS-CoV-2 infection, researchers are taking advantage of “omics” technologies to profile the expression of coronavirus entry factors across the tissues/cells and also to measure the host transcriptional response after virus infection. Two studies profiled expression after SARS-CoV-2 infection in multiple human cell lines (Figure 2A) [142,143]. The first study, which is by Blanco-Melo et al., performed an in-depth analysis of the transcriptional response to SARS-CoV-2 in comparison to other respiratory viruses, including MERS-CoV, SARS-CoV, human parainfluenza virus 3 (HPIV3), respiratory syncytial virus (RSV), and influenza A virus (IAV). They analyzed the responses of three human cell lines: A549 (adenocarcinomic human alveolar basal epithelial cells), Calu-3 (human airway epithelial cells derived from human bronchial submucosal glands), and MRC-5 (human fetal lung fibroblast cells). As the viral receptor ACE2 has low expression in A549 cells, authors also supplemented A549 cells with adenovirus (AdV)-based vectors expressing mCherry (a fluorescent protein used as a control) or ACE2 (A549-ACE2). All infections were performed at a high multiplicity of infections (MOI, 2–5), with the exception of A549-ACE2 cells, which were infected with SARS-CoV-2 at both low (0.2 MOI) and high MOI (2 MOI). Poly(A) bulk RNA sequencing (RNA-seq) of host cells was performed at 24 hours post-infection (hpi) of all the viruses except IAV (9–12 hours). The authors also measured host transcriptional responses to SARS-CoV-2 in primary normal human bronchial epithelial cells (HBEC or NHBE cells), nasal washes of ferrets as an animal model, and lung samples from two COVID-19 patients. Additionally, they measured transcriptional responses to IAV in NHBE cells and nasal washes of ferrets. Differential expression (DE) analysis was then carried out to compare infected cells with control cells that underwent only a mock treatment. In general, the interferons (IFNs) activate intracellular antimicrobial programs and are the major first line of defense against viruses [88]. IFNs are a type of cytokines along with chemokines, interleukins (IL), lymphokines and tumor necrosis factor (TNF). Cytokines can be classified based on the nature of the immune response or based on their specific roles, as reviewed by [144]. In the hosts where SARS-CoV-2 was able to replicate efficiently, DE analysis revealed that the transcriptional response was significantly different from the response to all of the other viruses tested. A unique proinflammatory cytokine signature associated with SARS-CoV-2 was present under both high- and low-MOI conditions. The cytokines IL-6 and IL1RA were uniquely elevated in response to SARS-CoV-2. However, A549-ACE2 cells in the low-MOI condition showed no significant IFN-I or IFN-III expression, but did in cells at high MOI. This finding suggests that IFN induction is MOI dependent. Similarly, in cells from the NHBE line, ferrets, and COVID-19 patients, they found significant enrichment of chemokine signaling but no significant induction of IFN-I or IFN-III. Together, these results suggest that in contrast to common respiratory viruses, SARS-CoV-2 induces a limited antiviral state with low IFN-I or IFN-III expression and a moderate IFN-stimulated genes (ISG) response. However, the low IFN induction in ACE2-expressing A549 cells could be overcome by using a 10-fold increase in SARS-CoV-2 (MOI, 2), suggesting a SARS-CoV-2 antagonist that is rendered ineffective under high-MOI conditions [142]. This hypothesis was further supported by a recent study [145] that showed that the SARS-CoV-2 *ORF3b* gene suppresses IFNB1 promoter activity (IFN-I induction) more efficiently than the SARS-CoV-ORF3b_ gene, which is considerably longer.

A second study by Wyler et al. [143] examined three human cell lines: H1299 (human non-small cell lung carcinoma cell line), Calu-3, and Caco-2 (human epithelial colorectal adenocarcinoma cell line). They performed a comprehensive analysis of the transcriptional response to SARS-CoV-2 and SARS-CoV at different hpi (4–36 hours) with an MOI of 0.3. Using poly(A) bulk RNA-seq, the authors found negligible susceptibility of H1299 cells (< 0.08 viral read percentage of total reads) in contrast to Caco-2 and Calu-3 cells (>10% of viral reads), suggesting a role of cell-type specific host factors. Based on visual inspection (microscopy images) and transcriptional profiling, the authors showed distinct responses associated with different hosts following infection. In contrast to Caco-2, SARS-CoV-2

infected Calu-3 cells showed signs of impaired growth and cell death at 24 hpi, as well as moderate IFN induction with a strong up-regulation of ISGs. Interestingly, the response is similar to SARS-CoV-2 infected Calu-3 cells at ~7-fold higher MOI performed by Blanco-Melo et al., suggesting that IFN induction is not MOI dependent in Calu-3 cells, in contrast to reports using A549-ACE2 cells. The discrepancy could be explained by the observations that Calu-3 cells are highly susceptible to SARS-CoV-2 with rapid virus replication [45], whereas A549 cells are incompatible with SARS-CoV-2 infection [146]. We performed a correlation analysis of the host expression response (RNA fold change compared to the mock infection) using the publicly available analyzed data from Blanco-Melo et al. and Wyler et al. (Figure 2B) [142,143]. In general, we found high correlations among the same host irrespective of the study and the virus infected, suggesting that the response is host-specific. For instance, Calu-3 cells infected with SARS-CoV by Wyler et al. and Calu-3 cells infected with SARS-CoV-2 by Blanco-Melo et al. had a Pearson's correlation coefficient of 0.8 (Figure 2B). Moreover, COVID-19 patients had the lowest correlations among all the cells used, with the highest value being 0.29. This discrepancy suggests that the *in vitro* models used may not necessarily imitate the human response, underscoring the importance of follow-up in additional models.

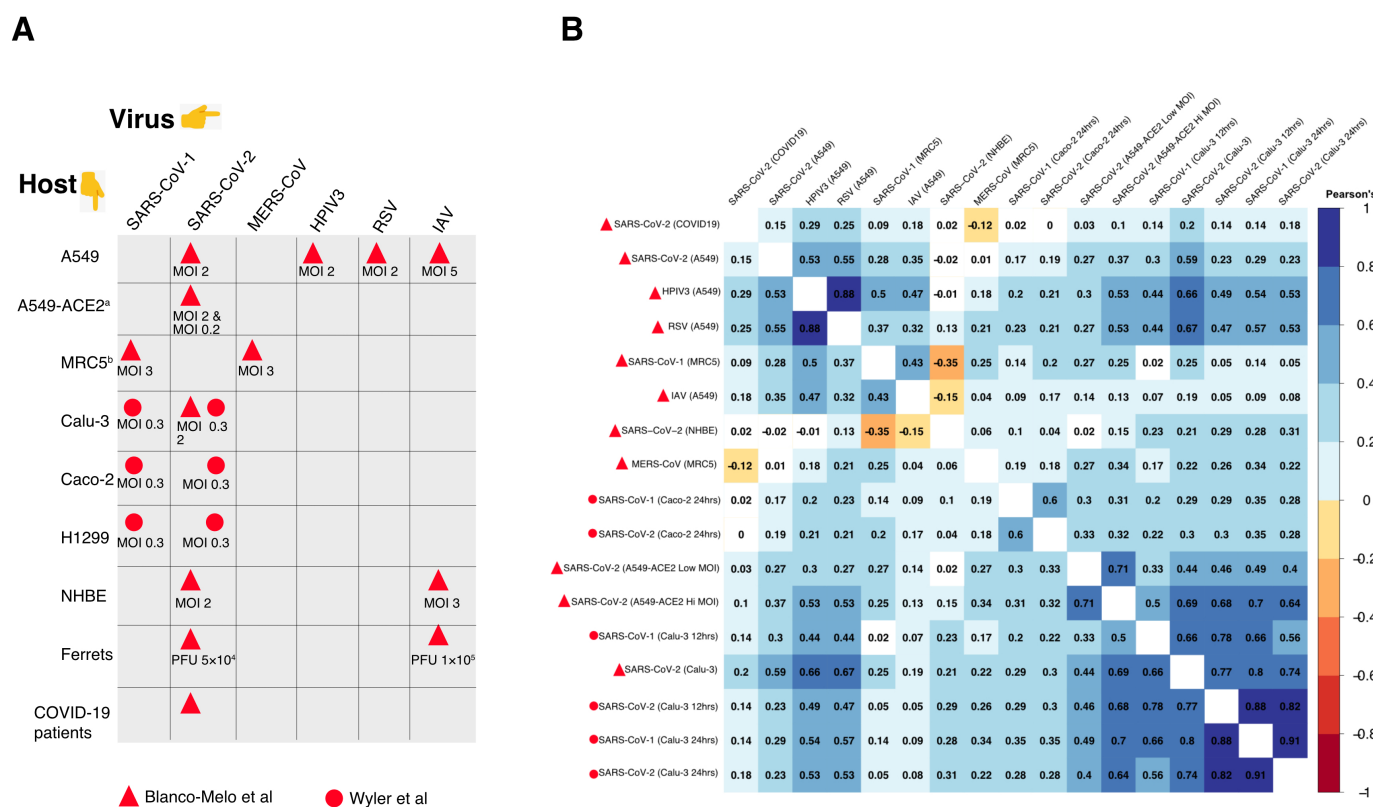


Figure 2: Profiling and correlation of expression response after respiratory viruses infection in various hosts. (A) Overview of hosts and respiratory viruses used in two studies [142,143]. MOI: Multiplicity of infections; PFU: Plaque-forming unit; a: ACE2-expressing A549 cells; b: Data used from GSE56192. (B) Pearson's correlation of expression response (Log2 fold change) between various hosts. Note that we used the data from bulk RNA-seq produced after the infection of unmodified viruses.

4 Transmission, Susceptibility, and Presentation

4.1 Mechanism of Transmission

In general, respiratory viruses like coronavirus can have multiple routes of person-to-person transmission including droplet transmission (i.e. inhalation for cough, sneeze), aerosol transmission (i.e. virus suspended in air), and contact transmission (i.e. contact with oral, nasal, and eye mucous membranes). These biological sources are considered to hold particular risk due to the pathogenesis of the virus (see below). Other modes of transmission, such as through touching surfaces or objects and then touching mucous membranes, can also be investigated. While droplet-based and contact were initially considered to be the primary modes of SARS-CoV-2 transmission [147], as additional information has emerged, the possibility of aerosol transmission has also been raised [148,149,150]. Other aspects of transmission to investigate are the relationship between infectiousness and virus shedding with disease period or symptoms and also the proportions of cases that are attributable to various types of transmission events, such as transmission between relatives, nosocomial transmissions, and other possible types of interactions. Some information about these characteristics of transmission are available for the highly pathogenic coronaviruses SARS-CoV and MERS-CoV [54,151]. For SARS-CoV-2 it is still being investigated whether, in addition to being spread by people who show symptoms, the virus can be transmitted by people who do not show symptoms [152], such as during the pre-symptomatic stage of infection or in people with asymptomatic infections. The current pandemic of COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), represents an acute global health crisis with symptoms for reported cases ranging from mild to severe or fatal [61] and including outcomes such as acute respiratory distress, acute lung injury and other pulmonary complications. The possibility of asymptomatic cases is also being investigated. The transmission and mortality rate estimations of COVID-19 are likely dynamic based on both public health and medical interventions.

4.2 Dynamics of Transmission

Disease spread dynamics can be estimated using R_0 , the basic reproduction number, and R_t , the effective reproduction number. Thus, accurate estimates are crucial to understanding the dynamics of infection and to predict the effects of different interventions. R_0 and the timescale of infection (measured by the infectious period and the exposed period) govern population-level epidemic dynamics, with R_0 being one of the most important epidemiological parameters [153]. R_0 is the average number of new (secondary) infections caused by one infected person, assuming a wholly susceptible population [154]. A simple mechanistic model used to describe infectious disease dynamics is a susceptible-infected-recovered (SIR) compartmental model. In this formulation individuals move through three states: susceptible, infected, and recovered; two parameters, γ and β , specify the rate at which the infectious recover, and the infection transmission rate, respectively. In this simple formulation, R_0 is estimated as the ratio of β and γ . [153,155]. A pathogen can invade a susceptible population only if $R_0 > 1$ [153,156]. The spread of an infectious disease at a particular time t can be quantified by R_t , the effective reproduction number, which assumes that part of the population has already recovered (and thus gained immunity to reinfection) or that mitigating interventions were put into place. For example, if only a fraction S_t of the population is still susceptible, $R_t = S_t \times R_0$. When R_t is greater than 1, an epidemic grows (i.e., the proportion of the population that is infectious increases); when R_t is less than 1, the proportion of the population that is infectious decreases. 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 SIR model and its extensions [157,158]. In the context of SARS-CoV-2, more complex modified susceptible-exposed-infectious-recovered (SEIR) models are commonly used.[need citations]

Estimates of R_0 for COVID-19 lie in the range $R_0=1.4-6.5$ [159,160,161]. Variation in R_0 is expected between different populations and the estimated values of R_0 discussed below are for specific populations in specific environments. The different estimates of R_0 should not necessarily be interpreted as a range of estimates of the same underlying parameter.

In one study of international cases, the predicted value is $R_0=1.7$ [162], in China (both Hubei province and nationwide), the value is predicted to lie in the range $R_0=2.0-3.6$ [159,163,164], and on a cruise ship where an outbreak occurred, predicted $R_0=2.28$ [165]. SEIR model-derived estimates of R_0 range from 2.0 - 6.5 in China [166,167,168,169] to $R_0=4.8$ in France [170]. Using the same model as for the French population, a study estimated $R_0=2.6$ in South Korea [170], which is consistent with other studies [171]. From a meta-analysis of studies estimating R_0 , [160] 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 [172]. 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) [161]. In South Korea, R_t was inferred for Feb-Mar 2020 in two cities: Daegu (the center of the outbreak), and Seoul [171]. 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. 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 were reported [173]. In Europe, analysis of 11 countries inferred the dynamics of R_t over a time range from the beginning of the outbreak until March 28, 2020, by which point most countries had implemented major interventions (such as school closures, public gathering bans, and stay-at-home orders) [174]. Across all countries, the mean R_t before interventions began was estimated as 3.87; R_t varied considerably, from below 3 in Norway to above 4.5 in Spain. After interventions, R_t decreased by an average of 64% across all countries, with mean $R_t=1.43$. The lowest predicted value was 0.97 for Norway and the highest was 2.64 for Sweden, which may be in part because Sweden did not implement social distancing measures on the same scale as other countries. The study concludes that while large changes in R_t are observed, it is too early to tell whether the interventions put into place are sufficient to decrease R_t below 1.

More generally, population-level epidemic dynamics can be both observed and modelled [155]. Data and empirically determined biological mechanisms inform models, while models can be used to try to understand data and systems of interest or to make predictions about possible future dynamics, such as the estimation of capacity needs [175] or the comparison of predicted outcomes among prevention and control strategies [176,177]. Many current efforts to model R_t have led to tools that assist the visualization of estimates in real time or over recent intervals [178,179]. While these may be valuable resources, it is important to note that the estimates arise from models containing many assumptions and are dependent on the quality of the data they use, which varies widely by region.

4.3 Factors Influencing Susceptibility

In the context of the United States, persons diagnosed with COVID-19 are more likely to require hospitalization if they are of male sex, of older age, and/or of Black/African American background [180,181]. African Americans have also been reported to have disproportionate risk of kidney complications from COVID-19 [107]. In addition to African Americans, disproportionate harm and mortality from COVID-19 has also been noted in Latino/Hispanic communities and in Native American / Alaskan Native communities such as the Navajo nation [182,183,184,185,186]. In Brazil, where the

pandemic has also been severe, indigenous communities are likewise at special risk [187]. The sizable racial disparities observed may be due to a number of factors, including different levels of pre-existing co-morbidities, such as hypertension, diabetes or lung diseases. They may also be influenced by the disproportionate socioeconomic burdens placed on many people of color, which can correspond to greater economic difficulties, more hazardous or crowded work or living conditions, or reduced access to health care [107,180,188]. This might cause infections to be less likely to be diagnosed unless or until they were very severe; in the sample studied by [180], African Americans were more likely to be diagnosed in hospital, while other groups were more likely to have been diagnosed in ambulatory settings in the community. More research is needed for analyzing and remediating these disparities [186].

People living in certain locations may be especially vulnerable to harm. In a preprint, [189] provided observational evidence that geographical areas in the United States that suffer from worse air pollution by fine particulate matter have also suffered more COVID-19 deaths per capita, after adjusting for demographic covariates. Although lack of individual-level exposure data and the impossibility of randomization make it difficult to elucidate the exact causal mechanism, this finding would be consistent with similar findings for all-cause mortality (e.g., [190]). Individuals in nursing homes / skilled nursing facilities [191] and in some prisons and detention centers [192,193] have also been exposed to higher risk of infection. Certain occupations, such as health care work, can put individuals at increased risk [194,195,196,197,198].

Many other factors influence risk of serious COVID-19 outcomes. Genetic factors may play a role in risk of respiratory failure for COVID-19 [199,200,201]. Diabetes may increase the risk of lengthy hospitalization [202] or of death [202,203]. [204] and [205] discuss possible ways in which COVID-19 and diabetes may interact. Obesity also appears to be associated with higher risk of severe outcomes from SARS-CoV-2 [206,207]. Obesity is considered an underlying risk factor for other health problems, and the mechanism for its contributions to COVID-19 hospitalization or mortality is not yet clear [208].

Studies of disparities and differences among groups in rates of hospitalization or death from COVID-19 are complicated by the fact that risk may be elevated in multiple ways. An individual may be more likely to be exposed to the virus, more likely to get infected once exposed, more likely to have serious complications once infected, be less likely to get adequate help once they are seriously ill. Although these are difficult to disaggregate, they suggest different possible interventions and each deserves consideration. The epidemiological characteristics and clinical presentation of COVID-19 may differ somewhat in different areas of the world, presumably due to differential reporting, different age structures, and/or different risk factors [203]. Furthermore, because different subpopulations may have somewhat different vulnerabilities, needs, and resources, we recommend that researchers publishing studies on diagnostics and therapeutics take extra care to be clear about the demographic and medical characteristics of their sample, in order to facilitate discussions of the degree to which results may generalize or differ in other settings.

Several studies on disparities in COVID-19 have compared groups in terms of their probability of a severe outcome (like hospitalization or death) given that a person is diagnosed. Early in the pandemic, it is more difficult to study or identify the larger population of all exposed or all infected people because of the existence of undetected infections; over the course of the pandemic, indirect estimates of infection rates through modeling improve and more direct estimates through a combination of serological tests, sampling methods and statistical methods have been made possible through biotechnology developments. In contrast, [209] were able to compare overall rates of death from COVID-19, not simply in the subsample of diagnosed individuals, thus combining the probability of infection with the probability of death given infection. This was done using a dataset of 17 million adults in the United Kingdom. In this administrative dataset, [209] found that male sex, older age, economic deprivation, nonwhite ethnicity (principally Black or South Asian), obesity, diabetes, asthma, and several other comorbid conditions were associated with a higher risk of death from COVID-19.

They cautioned that despite the large sample size, their observational data did not directly provide information on the causal mechanisms which led to these statistical associations. However, the ethnic and economic disparities did not vanish when adjusting for observed preexisting conditions. [209] also found that the predictive value of socioeconomic status seemed to increase over time, perhaps because many higher-paid workers were able to transition to working online.

Besides the direct harms caused by infection, many populations are in indirect risk of serious harm due to the social and economic effects of the pandemic and of the efforts needed to fight it. These might include individuals with substance use disorder [210], victims of natural disasters [211], and victims of human trafficking [212]. The pandemic could also delay the fight against other major infectious diseases, such as HIV, malaria and tuberculosis, potentially leading to a further increase of mortality [213]. Although they are beyond the scope of this paper, further research is needed in order to prevent these harms.

5 Diagnostics

Identifying individuals who have contracted COVID-19 is crucial to slowing down the global pandemic. Given the high transmissibility of SARS-CoV-2, the development of reliable assays to detect SARS-CoV-2 infection even in asymptomatic carriers is vitally important. For instance, the deployment of wide-scale diagnostic testing followed by the isolation of infected people has been a key factor in South Korea's successful strategy for controlling the spread of the virus. Following the first release of the genetic sequence of the virus by Chinese officials on January 10 2020, the first test was released about 13 days later [214]. A range of diagnostic approaches from a methodological standpoint are being or could possibly be developed.

There are two main classes of diagnostic tests: molecular tests, which can diagnose an active infection by identifying the presence of SARS-CoV-2, and serological tests, which can assess whether an individual was infected in the past via the presence or absence of antibodies against SARS-CoV-2. Molecular tests are essential for identifying individuals for treatment and alerting their contacts to quarantine and be alert for possible symptoms. While serological tests may be of interest to individuals who wish to confirm they were infected with SARS-CoV-2 in the past based on disease symptoms, their potential for false positives means that they are not currently recommended for this use. However, serological tests are critical at the population level from an epidemiological perspective, as they can be used to estimate the extent of the infection in a given area. Thus, they may be used to better understand the percent of infected cases that develop severe disease as well as to guide public health and economic decisions regarding resource allocation and counter-disease measures.

5.1 Molecular Tests

Molecular tests are used to identify distinct genomic subsequences of a viral molecule in a sample and thus to diagnose an active viral infection. This first requires identifying biospecimens that are likely to contain the virus in infected individuals and then acquiring these samples from the patient(s) to be tested. Common sources for a sample used in a molecular test include nasopharyngeal cavity samples, including throat wash and saliva [215], or stool samples [216]. Given a sample from a patient, molecular tests involve a number of steps to analyze a sample and produce results. When testing for RNA viruses like SARS-CoV-2, pre-processing is needed in order to create DNA, which can then be replicated during PCR, from the initial RNA sample. The DNA can then be amplified with PCR. Some tests use the results of the PCR to determine presence or absence of the pathogen, but in other cases, it may be necessary to sequence the amplified DNA. Sequencing requires an additional pre-processing step: library preparation. Library preparation is the process of preparing the sample for sequencing, typically by fragmenting the sequences and adding adapters [217]. In some cases, library preparation can involve other modifications of the sample, such as adding "barcoding" to identify a

particular sample in the sequence data, which is useful for pooling samples from multiple sources. There are different reagents used for library preparation that are specific to identifying one or more target sections with PCR [218]. Sequential pattern matching is then used to identify unique subsequences of the virus that identify it in specific. If sufficient subsequences are found, the test is considered positive.

5.1.1 RT-PCR

Real-Time Polymerase Chain Reaction (RT-PCR) tests determine whether a target is present by measuring the rate of amplification during PCR compared to a standard. When the target is RNA, such as in the case of RNA viruses, the RNA must be converted into complementary DNA during pre-processing. There are different reagents used for library preparation that are specific to identifying one or more target sections with PCR [218]. The Drosten Lab, from Germany, was the first lab to establish and validate a diagnostic test to detect SARS-CoV-2. This test uses RT-PCR with reverse transcription [214] to detect several regions of the viral genome: the *ORF1b* of the RNA dependent RNA polymerase (RdRP), the Envelope protein gene (*E*), and the Nucleocapsid protein gene (*M*). In collaboration with several other labs in Europe and in China, the researchers confirmed the specificity of this test with respect to other coronaviruses against specimens from 297 patients infected with a broad range of respiratory agents. Specifically this test utilizes two probes against RdRP of which one is specific to SARS-CoV-2 [214]. Importantly, this assay did not give any false positive results.

5.1.2 qRT-PCR

Chinese researchers developed a quantitative real-time reverse transcription PCR (qRT-PCR) test to identify two gene regions of the viral genome, *ORF1b* and *N* [219]. Specifically, this assay was tested on samples coming from two COVID-19 patients, including a panel of positive and negative controls consisting of RNA extracted from several cultured viruses. The assay uses the *N* gene to screen patients, while the *ORF1b* gene region is used to confirm the infection [219]. In this case the test was designed to detect sequences conserved across sarbecoviruses, or viruses within the same subgenus as SARS-CoV-2. Considering that no other sarbecoviruses are currently known to infect humans, a positive test indicates that the patient is infected with SARS-CoV-2. However, this test is not able to discriminate the genetics of viruses within the sarbecovirus clade.

5.1.2.1 dPCR

Digital PCR (dPCR) is a new generation of PCR technologies offering an alternative to traditional real-time quantitative PCR. In dPCR, a sample is partitioned into thousands of compartments, such as nanodroplets (droplet dPCR or ddPCR) or nanowells, and a PCR reaction takes place in each compartment. This leads to a digital read-out where each partition is either positive or negative for the nucleic acid sequence being tested for, allowing for much higher throughput. While dPCR equipment is not yet as common as that for RT-PCR, dPCR for DNA targets generally achieves higher sensitivity than other PCR technologies while maintaining high specificity, though sensitivity is slightly lower for RNA targets [220]. High sensitivity is particularly relevant for SARS-CoV-2 detection, since low viral load in clinical samples can lead to false negatives. Suo et al. performed a double-blind evaluation of ddPCR for SARS-CoV-2 detection on 57 samples–43 samples from suspected positive patients, and 14 from supposed convalescents–that had all tested negative for SARS-CoV-2 using RT-PCR. Despite the initial negative results, 33 out of 35 (94.3%) patients were later clinically confirmed positive. All of these individuals tested positive using ddPCR. Additionally, of 14 supposed convalescents who had received two consecutive negative RT-PCR tests, nine (64.2%) tested positive for SARS-CoV-2 using ddPCR. Two symptomatic patients tested negative with both RT-PCR and ddPCR, but were later clinically diagnosed positive, and 5 of the 14 suspected convalescents tested negative by ddPCR [221]. While not a complete head-to-head comparison to RT-PCR in all aspects– e.g. no samples testing positive using RT-PCR were evaluated by ddPCR– the study shows the potential of

ddPCR for viral detection in highly diluted samples. In a second study, Dong et al. [222] compared the results of qRT-PCR and ddPCR testing for SARS-CoV-2 in 194 samples, including 103 samples from suspected patients, 75 from contacts and close contacts, and 16 from suspected convalescents. Of the 103 suspected patient samples, 29 were reported as positive, 25 as negative, and 49 as suspected by qRT-PCR; all patients were later confirmed to be SARS-CoV-2 positive. Of the qRT-PCR negative or suspected samples, a total of 61 (17 negative and 44 suspected) were later confirmed to be positive by ddPCR, improving the overall detection rate among these patients from 28.2% to 87.4%. Of 75 patient samples from contacts and close contacts, 48 were tested negative with both methods and patients indeed remained healthy. Within the remaining 27 patient samples, 10 tested positive, 1 negative, 16 suspect by qRT-PCR. 15 out of 16 suspect samples and the negative test result were overturned by ddPCR, decreasing the rate of suspect cases from 21% to 1%. Importantly, all samples that tested positive using qRT-PCR also tested positive using ddPCR. Among the 16 convalescent patients, qRT-PCR identified 12 as positive, three as suspect, and one as negative, but RT-dPCR identified all 16 as positive. This evidence further indicates that the lower limit of detection made possible by ddPCR may be useful for identifying when COVID-19 patients are cleared of the virus. Overall, these studies suggest that dPCR is a promising tool for overcoming the problem of false-negative SARS-CoV-2 testing.

5.1.3 Pooled and Automated PCR Testing

Due to limited supplies and the need for more tests, several labs have found ways to pool or otherwise strategically design tests to increase throughput. The first such result came from Yelin et al. [223], who found they could pool up to 32 samples in a single qPCR run. This was followed by larger-scale pooling with slightly different methods [224]. Although these approaches are also PCR based, they allow for more rapid scaling and higher efficiency for testing than the initial PCR-based methods developed.

5.1.3.1 CRISPR-based detection

Two CRISPR-associated nucleases, Cas12 and Cas13, have been used for nucleic acid detection. Multiple assays exploiting these nucleases have emerged as potential diagnostic tools for the rapid detection of SARS-CoV-2 genetic material and therefore SARS-CoV-2 infection.

The SHERLOCK method (Specific High-sensitivity Enzymatic Reporter unLOCKing) from Sherlock Biosciences relies on Cas13a to discriminate between inputs that differ by a single nucleotide at very low concentrations [225]. The target RNA is amplified by RT-RPA and T7 transcription, and the amplified product activates Cas13a. The nuclease then cleaves a reporter RNA, which liberates a fluorescent dye from a quencher. Several groups have used the SHERLOCK method to detect SARS-CoV-2 viral RNA. An early study reported that the method could detect 7.5 copies of viral RNA in all 10 replicates, 2.5 copies in 6 out of 10, and 1.25 copies in 2 out of 10 runs [226]. It also reported 100% specificity and sensitivity on 114 RNA samples from clinical respiratory samples (61 suspected cases, among which 52 were confirmed and 9 ruled out by metagenomic next-generation sequencing, 17 nCoV-/hCoV+ cases and 36 samples from healthy subjects), and a reaction turn-around time of 40 minutes. A separate study screened four designs of SHERLOCK and extensively tested the best-performing assay. They determined the limit of detection to be 10 copies/ μ l using both fluorescent and lateral flow detection [227]. Lateral flow test strips are simple to use and read, but there are limitations in terms of availability and cost per test. Another group therefore proposed the CREST protocol (Cas13-based, Rugged, Equitable, Scalable Testing), which uses a P51 cardboard fluorescence visualizer, powered by a 9V battery, for the detection of Cas13 activity instead of immunochromatography [228]. CREST can be run, from RNA sample to result, with no need for AC power or a dedicated facility, with minimal handling in approximately 2 hours. Testing was performed on 14 nasopharyngeal swabs. CREST picked up the same positives as the CDC-recommended TaqMan assay with the exception of one borderline sample that displayed low quality RNA.

The DETECTR method (DNA Endonuclease-Targeted CRISPR Trans Reporter) from Mammoth Biosciences involves purification of RNA extracted from patient specimens, amplification of extracted RNAs by loop-mediated amplification, a rapid, isothermal nucleic acid amplification technique, and application of their Cas12-based technology. In their assay, guide RNAs were designed to recognize portions of sequences corresponding to the SARS-CoV-2 genome, specifically the N2 and E regions [229]. In the presence of SARS-CoV-2 genetic material, sequence recognition by the guide RNAs results in double-stranded DNA cleavage by Cas12, as well as cleavage of a single-stranded DNA molecular beacon. The cleavage of this molecular beacon acts as a colorimetric reporter that is subsequently read out in a lateral flow assay and indicates the positive presence of SARS-CoV-2 genetic material and therefore SARS-CoV-2 infection. The 40-minute assay is considered positive if there is detection of both the E and N genes or presumptive positive if there is detection of either of them. The assay had 95% positive predictive agreement and 100% negative predictive agreement with the US Centers for Disease Control and Prevention SARS-CoV-2 real-time RT-PCR assay. The estimated limit of detection was 10 copies per μl reaction, versus 1 copy per μl reaction for the CDC assay. These results have been confirmed by other DETECTR approaches. Using RTRPA for amplification, another group detected 10 copies of synthetic SARS-CoV-2 RNA per μl of input within 60 minutes of RNA sample preparation in a proof-of-principle evaluation [230]. The DETECTR protocol was improved by combining RT-RPA and CRISPR-based detection in a one-pot reaction that incubates at a single temperature, and by using dual crRNAs (which increases sensitivity). This new assay, known as All-In-One Dual CRISPR-Cas12a (AIOD-CRISPR), detected 4.6 copies of SARS-CoV-2 RNA per μl of input in 40 minutes [231]. Another single-tube, constant-temperature approach using Cas12b instead of Cas12a achieved a detection limit of 5 copies/ μl in 40-60 minutes [232]. It was also reported that that electric field gradients can be used to control and accelerate CRISPR assays by co-focusing Cas12-gRNA, reporters, and target [233]. The authors generated an appropriate electric field gradient using a selective ionic focusing technique known as isotachophoresis (ITP) implemented on a microfluidic chip. They also used ITP for automated purification of target RNA from raw nasopharyngeal swab samples. Combining this ITP purification with loop-mediated isothermal amplification, their ITP-enhanced assay to achieved detection of SARS-CoV-2 RNA (from raw sample to result) in 30 minutes.

There is an increasing body of evidence that CRISPR-based assays offer a practical solution for rapid, low-barrier testing in areas that are at greater risk of infection, such as airports and local community hospitals. In the largest study to date, DETECTR was compared to qRT-PCR on 378 patient samples [234]. The authors reported a 95% reproducibility. Both techniques were equally sensitive in detecting SARS-CoV-2. Lateral flow strips showed a 100% correlation to the high-throughput DETECTR assay. Importantly, DETECTR was 100% specific for SARS-CoV-2 and did not detect other human coronaviruses.

5.1.4 Limitation of Molecular Tests

Tests that identify SARS-CoV-2 using nucleic-acid-based technologies will identify only individuals with current infections and are not appropriate for identifying individuals who have recovered from a previous infection. Within this category, different types of tests have different limitations. For example, PCR-based test can be highly sensitive, but in high-throughput settings they can show several problems:

1. False-negative responses, which can present a significant problem to large-scale testing. To reduce occurrence of false negatives, correct execution of the analysis is crucial [235].
2. Uncertainty surrounding the SARS-CoV-2 viral shedding kinetics, which could affect the result of a test depending on when it was taken [235].
3. Type of specimen, as it is not clear which clinical samples are best to detect the virus [235].
4. Expensive machinery, which might be present in major hospitals and/or diagnostic centers but is often not available to smaller facilities [236].
5. Timing of the test, which might take up to 4 days to give results [236].

6. The availability of supplies for testing, including swabs and testing media, has been limited [237].
7. Because the guide RNA can recognize other interspersed sequences on the patient's genome, false positives and a loss of specificity can occur.

Similarly, in tests that use CRISPR, false positives can occur due to the specificity of the technique, as the guide RNA can recognize other interspersed sequences on the patient's genome. As noted above, false negatives are a significant concern for several reasons. Importantly, clinical reports indicate that it is imperative to exercise caution when interpreting the results of molecular tests for SARS-CoV-2 because negative results do not necessarily mean a patient is virus-free [238].

5.2 Serological Tests

Although diagnostic tests based on the detection of the genetic material can be quite sensitive, they cannot provide information about the extent of the disease over time. Most importantly, they would not work on a patient who has fully recovered from the virus at the time of sample collection. In this context, serological tests, which use serum to test for the presence of antibodies against SARS-CoV-2, are significantly more informative. Additionally, they can help scientists to understand why the disease has a different course among patients, as well as what strategy might work to manage the spread of the infection. Furthermore, serological tests hold significant interest at present because they can provide information relevant to advancing economic recovery and allowing reopenings. For instance, people that have developed antibodies can plausibly return to work prior to the others, based on (still-unproven) protective immunity [239]. On a related note, for some infectious agents an epidemic can be stopped from growing through herd immunity in which enough of the population is immune to infection through vaccination and/or prior experience with infection. A simple SIR model predicts that to achieve the required level of exposure for herd immunity to be effective, at least $(1 - (1/R_0))$ fraction of the population must be immune or, equivalently, less than $(1/R_0)$ fraction of the population susceptible [156]. However, for SARS-CoV-2 and COVID-19, because of the calculated R_0 and mortality and the recorded per-region deaths and accumulated cases with the estimated factor of undetected cases, relying on herd immunity without vaccines and/or proven treatment options and/or strong non-pharmaceutical measures of prevention and control would likely result in a significant loss of life.

5.2.1 Current Approaches

Several countries are now focused on implementing antibody tests, and in the United States, the FDA recently approved a serological test by Cellex for use under emergency conditions [240]. Specifically, the Cellex qSARS-CoV-2 IgG/IgM Rapid Test is a chromatographic immunoassay designed to qualitatively detect IgM and IgG antibodies against SARS-CoV-2 in the plasma of patients (blood sample) suspected to have developed the infection [240]. Such tests allow for the progress of the viral disease to be understood, as IgM are the first antibodies produced by the body and indicate that the infection is active. Once the body has responded to the infection, IgG are produced and gradually replace IgM, indicating that the body has developed immunogenic memory [241]. The test cassette contains a pad of SARS-CoV-2 antigens and a nitrocellulose strip with lines for each of IgG and IgM, as well as a control (goat IgG) [240]. In a specimen that contains antibodies against the SARS-CoV-2 antigen, the antibodies will bind to the strip and be captured by the IgM and/or IgG line(s), resulting in a change of color [240]. With this particular assay results can be read within 15-20 minutes [240]. Other research groups, such as the Krammer lab of the Icahn School of Medicine at Mount Sinai proposed an ELISA test that detects IgG and IgM that react against the receptor binding domain (RBD) of the spike proteins (S) of the virus [242]. The authors are now working to get the assay into clinical use [243].

5.2.2 Limitations of Serological Tests

Importantly, false-positives can occur due to the cross-reactivity with other antibodies according to the clinical condition of the patient [240]. Therefore, this test should be used in combination with RNA detection tests [240]. Due to the long incubation times and delayed immune responses of infected patients, serological tests are insufficiently sensitive for a diagnosis in the early stages of an infection. The limitations due to timing make serological tests far less useful for enabling test-and-trace strategies.

5.3 Possible Alternatives to Current Practices for Identifying Active Cases

Clinical symptoms are too similar to other types of pneumonia to be sufficient as a sole diagnostics criterion. In addition, as noted above, identifying asymptomatic cases is critical. Even among mildly symptomatic patients, a predictive model based on clinical symptoms had a sensitivity of only 56% and a specificity of 91% [244]. More problematic is that clinical symptom-based tests are only able to identify already symptomatic cases, not presymptomatic or asymptomatic cases. They may still be important for clinical practice, and for reducing tests needed for patients deemed unlikely to have COVID-19.

X-ray diagnostics have been reported to have high sensitivity but low specificity in some studies [245]. Other studies have shown that specificity varies between radiologists [246], though the sensitivity reported here was lower than that published in the previous paper. However, preliminary machine-learning results have shown far higher sensitivity and specificity from analyzing chest X-rays than was possible with clinical examination [247]. X-ray tests with machine learning can potentially detect asymptomatic or presymptomatic infections that show lung manifestations. This approach would still not recognize entirely asymptomatic cases. Given the above, the widespread use of X-ray tests on otherwise healthy adults is likely inadvisable.

5.4 Challenges to Diagnostic Approaches

5.4.1 Limitations to Implementation of Large-Scale Testing

More information to follow.

5.4.2 Strategies and Considerations for Determining Whom to Test

Currently, Coronavirus tests are limited to people that are in danger of serious illness [248]. Specifically, the individuals at risk include:

- people with severe symptoms
- people showing mild symptoms that have been in contact with a person who has developed the infection
- people with underlying health conditions

However, this method of testing administration does not detect a high proportion of infections and does not allow for test-and-trace methods to be used. Individuals who are asymptomatic (i.e. potential spreaders) and individuals who are able to recover at home are therefore often unaware of their status. For instance, a recent study from Imperial College estimates that in Italy the true number of infections is around 5.9 million in a total population ~60 million, compared to the 70,000 detected as of March 28th [174]. Another analysis, which examined New York state, indicated that as of May 2020, approximately 300,000 cases had been reported in a total population of approximately 20 million, corresponding to ~1.5% of the population, but ~12% of individuals sampled statewide were estimated as positive through antibody tests (along with indications of spatial heterogeneity at higher resolution) [249].

6 Therapeutics and Prophylactics

Given the observed and predicted spread of COVID-19, the development of interventions will be critical to mitigating its effect on health and the mortality rate. Such interventions fall into two categories: therapeutics, which are meant to treat an already existing disease, and prophylactics, which are meant to prevent a disease from occurring. For infectious diseases such as COVID-19, the main prophylactics are vaccines; several types of vaccines are currently under development, as detailed below. While vaccines would be expected to save the largest number of lives by bolstering the immune response of the at-risk population broadly to the virus, which would result in a lower rate of infection, the vaccine development process is long, and they fail to provide immediate prophylactic protection or treat ongoing infections [250]. This means that there is also an immediate need for treatments that palliate symptoms to avoid the most severe outcomes from infection. Therapeutics can generally either be considered for the treatment and reduction of symptoms — to reduce the severity and risks associated with an active infection — or as a more direct way of targeting the virus (“antivirals”) — to inhibit the development of the virus once an individual is infected. In the context of COVID-19, there is uncertainty surrounding the exact mechanism of action, as most therapies have secondary or off-target effects. Thus, for this section, we will classify both therapeutics and prophylactics according to their biological properties, specifically whether they are biologics (produced from components of organisms) or small molecules. Biologics include antibodies, interferons, and vaccines, while small molecules include drugs targeted at viral particles, drugs targeted at host proteins, and broad-based pharmaceuticals. Broad-based pharmaceuticals include the much-discussed drugs hydroxychloroquine and chloroquine. We also describe nutraceuticals, which are dietary supplement interventions that may prime an individual’s immune system to lessen the impact of RNA virus infections [251, 252]. In the following sections, we critically appraise the literature and clinical trials (Figure 3) surrounding the repurposing of existing treatments and development of novel approaches for the prevention, mitigation, and treatment of coronavirus infections.

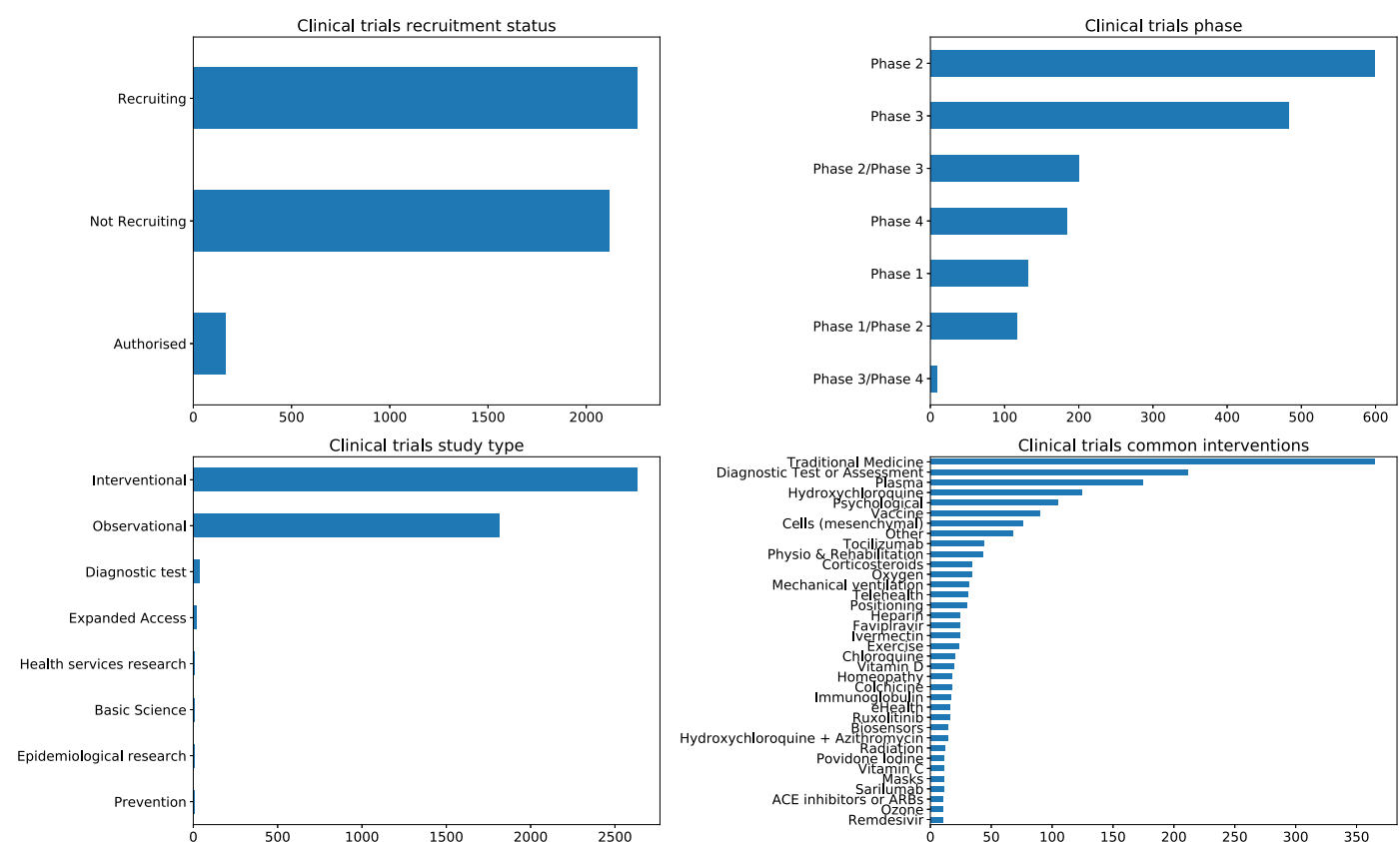


Figure 3: COVID-19 clinical trials. There are 4,550 COVID-19 clinical trials and 105 trials with results as of July 28, 2020. The recruitment statuses and trial phases are shown only for trials in which the status or phase is recorded. The study

types include only types used in at least five trials. The common interventions are all interventions used in at least ten trials. Combinations of interventions, such as Hydroxychloroquine + Azithromycin, are tallied separately from the individual interventions. Trials data are from the University of Oxford Evidence-Based Medicine Data Lab's COVID-19 TrialsTracker [[253](#)].

6.1 Treatment of Symptoms

The clinical picture of SARS-CoV-2 infection differs dramatically between individuals. Some are asymptomatic, and many experience mild COVID-19 symptoms. Mild symptoms commonly include fever and respiratory symptoms such as cough and sore throat, and, less commonly, gastrointestinal symptoms such as loss of appetite and vomiting [[254](#)]; some patients experience a combination of respiratory and gastrointestinal symptoms. The most severe cases of COVID-19 include severe complications such as pneumonia and Acute Respiratory Distress Syndrome (ARDS), which can lead to respiratory failure and death [[255](#)]. Thus, specific drugs may be considered to alleviate these severe symptoms and reduce the risk of death.

6.2 Small Molecule Drugs

6.2.1 Small Molecule Drugs for Targeting SARS-CoV-2

The replication cycle of a virus within an epithelial host cell includes six basic steps that can be summarized as follows: 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 [[256](#)]. 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 replication of viral genetic material. Importantly, SARS-CoV-2 is an RNA virus. In contrast to DNA viruses, which can use the host enzymes to propagate themselves, RNA viruses depends on their own polymerase, the RNA-dependent RNA polymerase (RdRP), for replication [[257](#),[258](#)]. As noted above, even if a drug is meant to target the virus, it can also impact other processes in the host.

6.2.1.1 Nucleoside and Nucleotide Analogs

6.2.1.1.1 Favipiravir

Favipiravir (Avigan) was discovered by Toyama Chemical Co., Ltd. [[259](#)]. The drug was found to effective at blocking viral amplification in several Influenza subtypes as well as other RNA viruses, such as Flaviviridae and Picornaviridae, through a reduction in plaque formation [[260](#)] and viral replication in MDCK cells [[261](#)]. Furthermore, inoculation of mice with favipiravir was shown to increase survivability. In 2014, the drug was approved in Japan for the treatment of patients infected with influenza that was resistant to conventional treatments like neuraminidase inhibitors [[262](#)].

Anticipated Mechanism. Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) acts as a purine and purine nucleoside analogue that inhibits viral RNA polymerase in a dose-dependent manner across a range of RNA viruses, including Influenza virus [[263](#),[264](#),[265](#),[266](#),[267](#)]. Nucleotide/side are the natural building blocks for RNA synthesis. Because of this, modifications to these nucleotides/sides can disrupt key processes including replication [[268](#)]. Biochemical experiments showed that favipiravir was recognized as a purine nucleoside analogue and incorporated into the viral RNA template. A single incorporation does not influence RNA transcription; however, multiple events of incorporation lead to the arrest of RNA synthesis [[269](#)]. Evidence for T-705 inhibiting viral

RNA polymerase are based on time-of-drug addition studies that found that viral loads were reduced with the addition of Favipiravir in early times post-infection [[263](#),[266](#),[267](#)].

Current Evidence. The effectiveness of favipiravir for treating patients with COVID-19 is currently under investigation. An open-label, nonrandomized, before-after controlled study was recently conducted [[270](#)]. The study included 80 COVID-19 patients (35 treated with favipiravir, 45 control) from the isolation ward of the National Clinical Research Center for Infectious Diseases (The Third People's Hospital of Shenzhen), Shenzhen, China. The patients in the control group were treated with other antivirals, such as lopinavir and ritonavir. Treatment was applied on days 2-14; treatment stopped either when viral clearance was confirmed or at day 14. The efficacy of the treatment was measured by 1) the time until viral clearance using Kaplan-Meier survival curves, and 2) the improvement rate of chest computed tomography (CT) scans on day 14 after treatment. The study found that favipiravir increased the speed of recovery (measured as viral clearance from the patient by RT-PCR) to 4 days compared to 11 days using other antivirals such as lopinavir and ritonavir. Additionally, the lung CT scans of patients treated with favipiravir showed significantly higher improvement rates (91%) on day 14 compared to control patients (62%). However, there were adverse side effects in 4 (11%) favipiravir-treated patients and 25 (56%) control patients. The adverse side effects included: diarrhea, vomiting, nausea, rash, and liver and kidney injury. Overall, despite the study reporting clinical improvement in favipiravir-treated patients, due to some issues with study design, it cannot be determined whether treatment with favipiravir had an effect or whether these patients would have recovered regardless of any treatment. For example, although there were significant differences between the two treatment groups, follow-up analysis is necessary due to the small sample size. The selection of patients did not take into consideration important factors such as previous clinical conditions or sex, and there was no age categorization. The study was not randomized or blinded, and the baseline control group was another antiviral instead of a placebo. Therefore, randomized controlled trials are still required.

6.2.1.1.2 Remdesivir

Remdesivir (GS-5734) was developed by Gilead Sciences to treat Ebola Virus Disease. At the outset of the COVID-19 pandemic, it did not have any FDA-approved use. However, on May 1, 2020, the FDA issued an Emergency Use Authorization (EUA) for remdesivir for the treatment of hospitalized COVID-19 patients [[271](#)]. The EUA was based on information from two clinical trials, NCT04280705 and NCT04292899 [[272](#),[273](#),[274](#),[275](#)].

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 [[276](#),[277](#),[278](#)]. Although it was developed against Ebola, it also inhibits polymerase and replication of the coronaviruses MERS-CoV and SARS-CoV in cell culture assays with submicromolar IC50s [[279](#)]. It also inhibits SARS-CoV-2, showing synergy with chloroquine *in vitro* [[278](#)].

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. 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 [[280](#)]. Remdesivir has also been reported to inhibit SARS-CoV-2 infection in a human cell line sensitive to the virus [[278](#)].

The effectiveness of remdesivir for treating patients with COVID-19 is currently under investigation. Remdesivir was first used on some COVID-19 patients under compassionate use guidelines [[281](#),[282](#)]. All were in late stages of COVID-19 infection, and these reports were inconclusive about the drug's efficacy. Gilead Sciences, the maker of remdesivir, led a recent publication that reported outcomes for

compassionate use of the drug in 61 patients hospitalized with confirmed COVID-19. Here, 200mg of remdesivir was administered intravenously on day 1, followed by a further 100mg/day for 9 days [275]. There were significant issues with the study design or lack thereof. There was no randomized control group. The inclusion criteria were variable: some patients only required low doses of oxygen, others required ventilation. The study included many sites, potentially with variable inclusion criteria and treatment protocols. Patients analyzed had mixed demographics. There was a short follow-up period of investigation. Some patients worsened, some patients died, and eight were excluded from the analysis mainly due to missing post-baseline information, thus their health is unaccounted for. Therefore, even though the study reported clinical improvement in 68% of the 53 patients ultimately evaluated, due to the significant issues with study design, it could not be determined whether treatment with remdesivir had an effect or whether these patients would have recovered regardless of treatment. Another study comparing 5 and 10 day treatment regimens had similar results but was also limited because of the lack of a placebo control [284]. The study did not alter our understanding of the efficacy of remdesivir in treating COVID-19, but the encouraging results motivated placebo controlled studies.

Remdesivir was later tested in a double-blind placebo-controlled phase 3 clinical trial performed at 60 trial sites, 45 of which were in the United states. The trial recruited 1,063 patients and randomly assigned them to placebo treatment or treatment with remdesivir. The treatment was 200 mg on day 1, followed by 100 mg on days 2 through 10. Data was analyzed from 1,059 patients (538 assigned to remdesivir and 521 to placebo). The two groups were well matched demographically and clinically at baseline. Those who received remdesivir had a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; $P < 0.001$). The Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). Though mortality was lower in the remdesivir group, it was not significant. Serious adverse events were reported for 114 of the 541 patients in the remdesivir group who underwent randomization (21.1%) and 141 of the 522 patients in the placebo group who underwent randomization (27.0%). The median time to recovery in patients in the subgroup receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) could not be established which may indicate that the follow up time was too short for this group (272 patients). Largely on the results of this trial, the FDA issued the Emergency Use Authorization (EUA) for remdesivir for the treatment of hospitalized COVID-19 patients.

As of July 2020, there are ten clinical trials underway using remdesivir to treat COVID-19 patients at both early and late stages of infection and in combinations with other drugs including [278,285,286,287,288].

Summary. Remdesivir is a first in class to receive FDA approval, currently as an Emergency Use Authorization. It establishes proof of principle that drugs targeting the virus can benefit patients. It also shows proof of principle that the virus can be targeted at the level of viral replication, since it targets the viral RNA polymerase at high potency. 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. Additional clinical trials of remdesivir on different patient pools and in combination with other therapies will refine its use in the clinic.

6.2.1.2 Protease Inhibitors

Several studies showed that viral proteases play an important role in the life cycle of (corona)viruses by modulating the cleavage of viral polyprotein precursors [289]. Several FDA-approved drugs target proteases, including lopinavir and ritonavir for HIV infection and simeprevir for hepatitis C virus infection. In particular, serine protease inhibitors were suggested for the treatment of SARS and MERS viruses [290]. Recently, a study [44] suggested that camostat mesylate, an FDA-approved protease inhibitor (PI) could block the entry of SARS-CoV-2 into lung cells in vitro. However, to test the efficacy of PIs in patients, randomized clinical trials have to be conducted on patients and healthy volunteers.

6.2.1.2.1 N3

N3 is an inhibitor of Mpro, a 33.8-kilodaltons (kDa) SARS-CoV-2 protease that is involved in viral replication and transcription.

Anticipated Mechanism. N3 inhibits Mpro through binding to its substrate pocket.

Current Evidence. N3 was first designed computationally [291] to bind in the substrate binding pocket of the Mpro protease of SARS-like coronaviruses [292]. Subsequently, the structure of N3-bound SARS-CoV-2 Mpro was solved [293], confirming the computational prediction. Finally, N3 reduced the viral load in samples taken from patients.

Summary. N3 is a computationally designed molecule that inhibits the viral transcription through inhibiting Mpro. Although N3 is a strong inhibitor of SARS-CoV-2 in vitro, its safety and efficacy have to be tested in healthy volunteers and patients.

6.2.1.2.2 Ebselen

Ebselen identified as Mpro protease inhibitor. It is currently investigated as an anti-oxidant drug [294].

Anticipated Mechanism. Ebselen inhibits Mpro through binding to its substrate pocket.

Current Evidence. After the design and confirmation of N3 as a highly potent Michael acceptor inhibitor and the identification of Mpro structure [293,295], 10,000 compounds were screened for their in vitro anti-Mpro activity. The six leads that were identified were Ebselen, Disulfiram, Tideglusib, Carmofour, PX-12. When the compounds were further assayed on patient viral samples, Ebselen had the strongest potency in reducing the viral load. However, the authors cautioned that these compounds are likely promiscuous binders, which would diminish their therapeutic potential.

Summary. Ebselen is both a strong Mpro inhibitor and strong inhibitor of viral replication in vitro. The reduction of the viral load after exposure to Ebselen was even larger than N3. Ebselen is a very promising compound since its safety has been demonstrated in other indications. However, Ebselen is likely a false positive since it is a promiscuous compound that can have many targets [296]. Therefore, compounds with higher specificity are required to effectively translate to clinical trials.

6.2.1.3 Molecules Targeting the Viral Envelope

Why it may be useful

6.2.2 Drugs Targeting Host Proteins

Brief background on the therapeutic.

6.2.2.1 Viral Entry Receptors

Entry of SARS-CoV-2 into the cell depends on the ACE2 receptor and the enzyme encoded by *TMPRSS2* [44]. In principle, drugs that reduce the expression of these proteins or sterically hinder viral interactions with them might reduce viral entry into cells.

Current Evidence. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are among the most commonly prescribed medications [297,298]. In the United States, for example, they are prescribed well over 100,000,000 times annually. Data from some animal models suggest several, but not all, ACE inhibitors and several ARBs increase ACE2 expression in the cells of some organs [299]. Clinical studies have not established whether plasma ACE2 expression is increased in humans treated with these medications [300]. While randomized clinical trials are ongoing, a variety of observational studies have examined the relationship between exposure to ACE inhibitors or ARBs and outcomes in patients with COVID-19. An observational study of the association of ACE inhibitor or ARB exposure on outcomes in COVID-19 was retracted from the *New England Journal of Medicine* [301]. Moreover, because observational studies are subject to confounding, randomized controlled trials are the standard means of assessing the effects of medications, and the findings of the various observational studies bearing on this topic cannot be interpreted as indicating a protective effect of the drug [302,303]. Clinical trials testing the effects of ACE inhibitors or ARBs on COVID-19 outcomes are ongoing [304,305,306,307,308,309]. These studies of randomized intervention will provide important data for understanding whether exposure to ACEis or ARBs is associated with COVID-19 outcomes. Additional information about ACE2, observational studies of ACE inhibitors and ARBs in COVID-19, and clinical trials on this topic have been summarized [310].

Summary. Summarize the state of the antiviral approach.

6.2.3 Broad-Spectrum Pharmaceuticals

- Add some background on broad-spectrum pharmaceuticals

6.2.3.1 Hydroxychloroquine and Chloroquine

Potential Mechanism. Chloroquine (CQ) and hydroxychloroquine (HCQ) are lysosomotropic agents, meaning they are weak bases that can pass through the plasma membrane. Both drugs increase cellular pH by accumulating in their protonated form inside lysosomes [311,312]. This shift in pH inhibits the breakdown of proteins and peptides by the lysosomes during the process of proteolysis [312]. A number of mechanisms have been proposed through which these drugs could influence the immune response to pathogen challenge. For example, CQ/HCQ can interfere with digestion of antigens within the lysosome and inhibit CD4 T-cell stimulation while promoting the stimulation of CD8 T-cells [312]. CQ/HCQ can also decrease the production of certain key cytokines involved in the immune response including IL-6 and inhibit the stimulation of toll-like receptors (TLR) and TLR signaling [312]. The drugs also have anti-inflammatory and photoprotective effects and may also affect rates of cell death, blood clotting, glucose tolerance, and cholesterol levels [312].

Interest in CQ and HCQ for treating COVID-19 was catalyzed by a mechanism observed in *in vitro* studies of both SARS-CoV and SARS-CoV-2. In one study, CQ inhibited viral entry of SARS-CoV into Vero E6 cells, a cell line derived from the epithelial cells of an African green monkey kidney, through the elevation of endosomal pH and the terminal glycosylation of angiotensin-converting enzyme 2 (ACE2), which is the cellular entry receptor [313]. Increased pH within the cell, as discussed above, inhibits proteolysis, and terminal glycosylation of ACE2 is thought to interfere with virus-receptor binding. An *in vitro* study of SARS-CoV-2 infection of Vero cells, a line from which the Vero E6 clone has been separated since 1968, found both HCQ and CQ to be effective in inhibiting viral replication, with HCQ being more potent [314]. Additionally, an early case study of three COVID-19 patients reported the presence of antiphospholipid antibodies in all three patients [114]. Antiphospholipid antibodies are

central to the diagnosis of the antiphospholipid syndrome, a disorder that HCQ has often been used to treat [315,316,317]. Together, these studies triggered initial enthusiasm about the therapeutic potential for HCQ and CQ against COVID-19. HCQ/CQ has been proposed both as a treatment for COVID-19 and a prophylaxis against SARS-CoV-2 exposure. Additionally, HCQ/CQ are sometimes administered with azithromycin (AZ) and/or zinc supplementation. This section will discuss the current information available on the administration of CQ and HCQ as a treatment for or prophylaxis against COVID-19.

Controversy. The initial study evaluating HCQ as a treatment for COVID-19 patients was published on March 20, 2020 by Gautret et al. This non-randomized, non-blinded, non-placebo clinical trial compared HCQ to standard of care in 42 hospitalized patients in southern France [318]. They reported that patients who received HCQ showed higher rates of virological clearance by nasopharyngeal swab on Days 3-6 when compared to standard care. This study also treated six patients with both HCQ + AZ and found this combination therapy to be more effective than HCQ alone. This study showed design and analysis weaknesses that severely limit interpretability of results, including the lack of randomization, lack of blinding, lack of placebo, lack of Intention-To-Treat analysis, lack of correction for sequential multiple comparisons, trial arms entirely confounded by hospital, false negatives in outcome measurements, lack of trial pre-registration, and small sample size. Two of these weaknesses are due to inappropriate data analysis and can therefore be corrected post-hoc by recalculating p-values (lack of Intention-To-Treat analysis and multiple comparisons.) However, all other weaknesses are fundamental design flaws and cannot be corrected for. Thus, conclusions cannot be generalized outside of the study. The International Society of Antimicrobial Chemotherapy, the scientific organization that publishes *International Journal of Antimicrobial Agents* where the article appeared, has announced that the article does not meet its expected standard for publications [319], although it has not been officially retracted. Because of the preliminary data presented in this study, the use of HCQ in COVID-19 treatment has subsequently been explored by other researchers. About one week later, a follow-up case study reported that 11 consecutive patients were treated with HCQ + AZ using the same dosing regimen [320]. One patient died, two were transferred to the ICU, and one developed a prolonged QT interval, leading to discontinuation of HCQ + AZ. As in the Gautret et al. study, the outcome assessed was virological clearance at Day 6 post-treatment, as measured in nasopharyngeal swabs. Of the ten living patients on Day 6, eight remained positive for SARS-CoV-2 RNA. Like in the original study, interpretability was severely limited by lack of comparison group and the small sample size. However, these results stand in contrast to the claims by Gautret et al. that all six patients treated with HCQ + AZ tested negative for SARS-CoV-2 RNA by Day 6 post-treatment. This case study illustrated the need for further investigation using robust study design before the original proposed benefits of HCQ could be widely accepted.

On April 10, 2020, a randomized, non-placebo trial of 62 COVID-19 patients at the Renmin Hospital of Wuhan University was released [321]. This study investigated whether HCQ decreased time to fever break or time to cough relief when compared to standard of care [321]. This trial found HCQ decreased both average time to fever break and average time to cough relief, defined as mild or no cough. While this study improved on some of the methodological flaws in Gautret et al. by randomizing patients, it also had several flaws in trial design and data analysis that prevent generalization of the results. These weaknesses include the lack of placebo, lack of correction for multiple primary outcomes, inappropriate choice of outcomes, lack of sufficient detail to understand analysis, drastic disparities between pre-registration and published protocol, and small sample size. The choice of outcomes may be inappropriate as both fevers and cough may break periodically without resolution of illness. Additionally, for these outcomes, the authors reported that 23 of 62 patients did not have a fever and 25 of 62 patients did not have a cough at the start of the study, but the authors failed to describe how these patients were included in a study assessing time to fever break and time to cough relief. It is important to note here that the authors claimed “neither the research performers nor the patients were aware of the treatment assignments.” This blinding seems impossible in a non-placebo trial because at the very least, providers would know whether they were

administering a medication or not, and this knowledge could lead to systematic differences in the administration of care. Correction for multiple primary outcomes can be adjusted post-hoc by recalculating p-values, but all of the other issues were design and statistical weaknesses that cannot be corrected for. Additionally, the observation of drastic disparities between pre-registration and published protocol could indicate p-hacking. The design limitations mean that the conclusions cannot be generalized outside of the study. A second randomized trial, conducted by the Shanghai Public Health Clinical Center, analyzed whether HCQ increased rates of virological clearance at day 7 in respiratory pharyngeal swabs compared to standard care [322]. This trial was published in Chinese along with an abstract in English, and only the English abstract was read and interpreted for this review. The trial found comparable outcomes in virological clearance rate, time to virological clearance, and time to body temperature normalization between the treatment and control groups. A known weakness is small sample size, with only 30 patients enrolled and 15 in each arm. This problem suggests the study is underpowered to detect potentially useful differences and precludes interpretation of results. Additionally, because only the abstract could be read, other design and analysis issues could be present. Thus, though these studies added randomization to their assessment of HCQ, their conclusions should be interpreted very cautiously. These two studies assessed different outcomes and reached differing conclusions about the efficacy of HCQ for treating COVID-19; the designs of both studies, especially with respect to sample size, meant that no general conclusions can be made about the efficacy of the drug.

Several widely reported studies on HCQ have issues with data integrity and/or provenance. A Letter to the Editor published in *BioScience Trends* on March 16, 2020 claimed that numerous clinical trials have shown that HCQ is superior to control treatment in inhibiting the exacerbation of COVID-19 pneumonia [323]. This letter has been cited by numerous primary literature, review articles, and media alike [324,325]. However, the letter referred to 15 pre-registration identifiers from the Chinese Clinical Trial Registry. When these identifiers are followed back to the registry, most trials claim they are not yet recruiting patients or are currently recruiting patients. For all of these 15 identifiers, no data uploads or links to publications could be located on the pre-registrations. At the very least, the lack of availability of the primary data means the claim that HCQ is efficacious against COVID-19 pneumonia cannot be verified. Similarly, a recent multinational registry analysis [326] analyzed the efficacy of CQ and HCQ with and without a macrolide, which is a class of antibiotics that includes Azithromycin, for the treatment of COVID-19. The study observed 96032 patients split into a control and four treatment conditions (CQ with and without a macrolide; HCQ with and without a macrolide). They concluded that treatment with CQ and HCQ was associated with increased risk of *de novo* ventricular arrhythmia during hospitalization. However, this study has since been retracted by *The Lancet* due to an inability to validate the data used [327]. These studies demonstrate that increased skepticism in evaluation of the HCQ/CQ and COVID-19 literature may be warranted, possible because of the significant attention HCQ and CQ have received as possible treatments for COVID-19 and the politicization of these drugs.

Despite the fact that the study suggesting that CQ/HCQ increased risk of ventricular arrhythmia in COVID-19 patients has now been retracted, previous studies have identified risks with HCQ/CQ. A patient with systemic lupus erythematosus developed a prolonged QT interval that was likely exacerbated by use of HCQ in combination with renal failure [328]. A prolonged QT interval is associated with ventricular arrhythmia [329]. Furthermore, a separate study [330] investigated the safety associated with the use of HCQ with and without macrolides between 2000 and 2020. The study involved 900,000 cases treated with HCQ and 300,000 cases treated with HCQ + AZ. The results indicated that short-term use of HCQ was not associated with additional risk, but that HCQ + AZ was associated with an enhanced risk of cardiovascular complications (15-20% increased risk of chest pain) and a two-fold increased risk of mortality. Therefore, whether studies utilize HCQ alone or HCQ in combination with a macrolide may be an important consideration in assessing risk. As results from initial investigations of these drug combinations have emerged, concerns about the efficacy and risks of treating COVID-19 with HCQ and CQ has led to the removal of CQ/HCQ from standard of care

practices in several countries [331,332]. As of May 25, 2020, WHO had suspended administration of HCQ as part of the worldwide Solidarity Trial [333].

Current Evidence. As additional research has emerged, it remains unclear whether HCQ and/or CQ affect COVID-19 outcomes. A randomized, open-label, non-placebo trial of 150 COVID-19 patients was conducted in parallel at 16 government-designated COVID-19 centers in China to assess the safety and efficacy of HCQ [334]. The trial compared treatment with HCQ in conjunction with standard of care (SOC) to SOC alone in 150 infected patients who were assigned randomly to the two groups (75 per group). The primary endpoint of the study was the negative conversion rate of SARS-CoV-2 in 28 days, and the investigators found no difference in this parameter between the groups. The secondary endpoints were an amelioration of the symptoms of the disease such as axillary temperature $\leq 36.6^{\circ}\text{C}$, SpO₂ >94% on room air, and disappearance of symptoms like shortness of breath, cough, and sore throat. The median time to symptom alleviation was similar across different conditions (19 days in HCQ+SOC vs. 21 days in SOC). However, the investigators reported an interesting finding revealed in *post hoc* analysis: controlling for the administration of antivirals yielded an effect of HCQ on the alleviation of symptoms, with a reported hazard ratio of 8.83, although the 95% confidence interval of 1.09 to 71.3 suggests that this analysis may be underpowered and should be interpreted cautiously, as only 28 patients total (14 in each group) met this criterion. Additionally, there was a non-significant trend towards a greater number of lymphocytes in the SOC+HCQ group compared to the SOC-alone group (mean of 0.062 versus 0.008; $p=0.57$). Given the improvement in CRP levels and the possible improvement in lymphocyte count, the authors hypothesized that the addition of HCQ to the current SOC could decrease the inflammatory response, which could help to prevent multiorgan failure and death. However, one of the key results of this trial was that the 30% of the patients receiving SOC+HCQ reported adverse outcomes compared to 8.8% of patients receiving only SOC. The most common adverse outcome in the SOC+HCQ group was diarrhea (10% vs. 0% in the SOC group, $p=0.004$).

The adverse effects of administering HCQ to mild and moderate COVID-19 cases were found to be manageable. Furthermore, there are several factors that limit the interpretability of this study. Most of the enrolled patients had mild-to-moderate symptoms (98%), and the average age was 46. Although the authors claimed that HCQ could be beneficial in hindering disease progression, multiorgan failure, and death in COVID-19, this finding cannot be extrapolated to older patients, who are known to be at higher risk, or to severe cases. Additionally, a larger sample size is needed to validate whether lymphocyte counts increase in patients treated with SOC+HCQ; although the result in the present analysis appeared promising, it lacked statistical significance. Likewise, in this study, SOC included the use of antivirals (Lopinavir-Ritonavir, Arbidol, Oseltamivir, Virazole, Entecavir, Ganciclovir, and Interferon alfa), which appeared to introduce confounding effects. Thus, to isolate the effect of HCQ, SOC would need to exclude the use of antivirals. In this trial, the samples used to test for the presence of the SARS-CoV-2 virus were collected from the upper respiratory tract, and the authors indicated that the use of upper respiratory samples may have introduced false negatives (e.g., [67]); thus, the identification of biomarkers that can be collected non-invasively would be valuable to studies such as this one. Another limitation of the study that the authors acknowledge was that the HCQ treatment began, on average, at a 16-day delay from the symptom onset. An investigation of earlier intervention with HCQ would help to elucidate how the drug affects early disease management. Overall, the study provides promising data, although all of the findings still need to be validated in independent population cohorts. The fact that this study was open-label and lacked a placebo limits interpretation, and additional analysis is required to determine whether HCQ reduces inflammatory response.

Additional evidence comes from a retrospective analysis [335] that examined data from 368 COVID-19 patients across all United States Veteran Health Administration medical centers. The study retrospectively investigated the effect of the administration of HCQ ($n=97$), HCQ + AZ ($n=113$), and no HCQ ($n=158$) on 368 patients. The primary outcomes assessed were death and the need for mechanical ventilation. Standard supportive care was rendered to all patients. Due to the low

representation of women (N=17) in the available data, the study included only men, and the median age was 65 years. The rate of death in the HCQ-only treatment condition was 27.8% and in the HCQ + AZ treatment condition, it was 22.1%. In comparison to the 14.1% rate of death in the no-HCQ cohort, these data indicated a statistically significant elevation in the risk of death for the HCQ-only group compared to the no-HCQ group (adjusted hazard ratio: 2.61, $p=0.03$), but not for the HCQ + AZ group compared to the no-HCQ group (adjusted hazard ratio: 1.14; $p=0.72$). Further, the risk of ventilation was similar across all three groups (adjusted hazard ratio: 1.43, $p=0.48$ (HCQ) and 0.43, $p=0.09$ (HCQ + AZ) compared to no HCQ). The study thus showed evidence of an association between increased mortality and HCQ in this cohort of COVID-19 patients but no change in rates of mechanical ventilation among the treatment conditions. The study had a few limitations: it was not randomized, and the baseline vital signs, laboratory tests, and prescription drug use were significantly different among the three groups. All of these factors could potentially influence treatment outcome. Furthermore, the authors acknowledge that the effect of the drugs might be different in females and pediatric subjects, since these subjects were not part of the study. The reported result that HCQ + AZ is safer than HCQ contradicts the findings of the previous large-scale analysis of twenty years of records that found HCQ + AZ to be more frequently associated with cardiac arrhythmia than HCQ alone [330]; whether this discrepancy is caused by the pathology of COVID-19, is influenced by age or sex, or is a statistical artifact is not presently known.

Thus, both of the above studies have significant limitations but analyzed data acquired broadly from centers within a country's health system in China and the United States, respectively. Neither study reported robust improvements in patients treated with HCQ, although the Tang et al. study identified potential improvements associated with HCQ in *post hoc* analysis. In contrast, the VA study found that HCQ was associated with increased risk of mortality in COVID-19 patients. These two studies examined different populations, especially since age and sex have both been found to influence the severity of COVID-19. Additional analyses to increase sample size and encompassing a variety of ages and sexes could help to resolve the potential benefits and risks of HCQ administration to COVID-19 patients. A randomized, blinded study with a placebo would serve to overcome many of the limitations in the design of these studies.

One study did utilize a randomized, double-blind, placebo-controlled design, although this study analyzed the administration of HCQ prophylactically rather than therapeutically [336]. Asymptomatic adults in the United States and Canada who had been exposed to SARS-CoV-2 within the past four days were enrolled in an online study to see whether administration of HCQ over five days would influence the probability of developing COVID-19 symptoms over a 14-day period. Of the participants, 414 received HCQ and 407 received a placebo. Other than location, the demographics of this study were more comparable to the Yang et al. study above, as 51.6% of participants were women and the median age was 40 years. They found no significant difference in the rate of symptomatic illness between the two groups (11.8% HCQ, 14.3% placebo, $p=0.35$). The HCQ condition was associated with side effects, with 40.1% of patients reporting side effects compared to 16.8% in the control group ($p<0.001$). However, likely due to the high enrollment of healthcare workers (66% of participants) and the well-known side effects associated with HCQ, a large number of participants were able to correctly identify whether they were receiving HCQ or a placebo (46.5% and 35.7%, respectively). Furthermore, due to a lack of availability of diagnostic testing, only 20 of the 107 cases were confirmed with a PCR-based test to be positive for SARS-CoV-2. The rest were categorized as "probable" or "possible" cases by a panel of four physicians who were blind to the treatment status. However, a patient presenting one or more symptoms, which included diarrhea, was defined as a "possible" case, but diarrhea is also a common side effect of HCQ. Additionally, four of the twenty PCR-confirmed cases did not develop symptoms until after the observation period had completed, suggesting that the 14-day trial period may not have been long enough or the initial exposure may not have accounted for secondary exposure, given that most of the patients were exposed through situations that were likely to be recurrent: by a close family member with a COVID-19 diagnosis or through their work in healthcare. Finally, in addition to the young age of the participants in this study, which ranged from 32 to 51, there

were possible impediments to generalization introduced by the selection process, as the 2,237 patients who were eligible but had already developed symptoms by day 4 were enrolled in a separate study. It is therefore likely that asymptomatic cases were over-represented in this sample, which would not have been detected based on the diagnostic criteria used. Therefore, while this study does represent the first effort to conduct a randomized, double-blind, placebo-controlled investigation of HCQ's effect on COVID-19 symptoms in a large sample, the lack of PCR tests significantly impedes interpretation of the results.

Summary. *In vitro* evidence suggests that HCQ may be an effective therapeutic against SARS-CoV-2 and COVID-19. Because the 90% effective concentration (EC₉₀) of CQ in Vero E6 cells (6.90 µM) can be achieved in and tolerated by rheumatoid arthritis patients, it was hypothesized that it might also be possible to achieve the effective concentration in COVID-19 patients [337]. Additionally, HCQ has been found to be effective in treating HIV [338] and chronic Hepatitis C [339] patients. Therefore, initially it was thought that CQ/HCQ could be effective against SARS-CoV-2. CQ and HCQ have both been found to inhibit the expression of CD154 in T-cells and to reduce toll-like receptor signaling that leads to the production of pro-inflammatory cytokines [340]. Clinical trials for COVID-19 have more often used HCQ rather than CQ because it offers the advantages of being cheaper and having fewer side effects than CQ. Several countries have removed CQ from their standard of care for COVID-19 due to the frequency of adverse effects. However, a large analysis of patients receiving HCQ from January 2000 through March 2020 reported that the combination of HCQ and azithromycin, but not other macrolides, was associated with an elevated risk of cardiovascular complications and mortality. Multiple clinical studies have already been carried out to assess HCQ as a therapeutic agent for COVID-19, and many more are in progress. To date, none of these studies have used randomized, double-blind, placebo-controlled designs with a large sample size, which would be the gold standard. The one exception was an analysis of the prophylactic potential of HCQ [336], which was designed to meet all these criteria, but masking was not adequately maintained during the study and the outcomes were not accurately assessed due to the lack of availability of PCR-based testing in the United States and Canada. Thus, interpretation is severely limited and must be done cautiously. Due to inconsistency in the outcomes assessed and results reported from study to study, it remains unclear whether HCQ, or HCQ + AZ as a combination therapy, holds any therapeutic or prophylactic value against COVID-19. Additionally, one study identified an increased risk of mortality in older men receiving HCQ, and administration of HCQ and HCQ+AZ did not decrease the use of mechanical ventilation in these patients [335]. HCQ use for COVID-19 also leads to shortages for anti-malarial or anti-rheumatic use, where it has been definitively proven to be effective. Further investigation of HCQ in large, rigorous, multi-center clinical trials encompassing different sex and ages is required.

6.2.4 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 [341,342]. The key difference between a dietary supplement and a nutraceutical is that nutraceuticals should not only supplement the diet, but they must also aid in the prophylaxis and/or treatment of a disorder or disease [343]. Unlike pharmaceuticals, nutraceuticals do not fall under the responsibility of the FDA, but they are monitored as dietary supplements according to the Dietary Supplement, Health and Education Act 1994 (DSHEA) [344] and the Drug Administration Modernization Act 1997 [345]. However, there is significant concern that these acts do not adequately protect the consumer as they ascribe responsibility on the manufacturers to ensure safety of the product before manufacturing or marketing [346]. Likewise, manufacturers are not required to register or seek approval from the FDA to produce or sell food supplements or nutraceuticals. Health or nutrient content claims for labeling purposes are approved based on an authoritative statement from the Academy of Sciences or relevant federal authorities once the FDA has been notified and on the basis that the information is known to be true and not deceptive [346]. In Europe, health claims are only permitted on a product

label following authorization according to the European Food Safety Authority (EFSA) guidelines on nutrition and health claims [347]. EFSA does not currently distinguish between food supplements and nutraceuticals for health claim applications of new products as claim authorization is dependent on the availability of clinical data in order to substantiate efficacy [348]. These guidelines seem to provide more protection to consumers. Currently, there is a debate among scientists and regulatory authorities to develop a regulatory framework in order to deal with the challenges of safety and health claim substantiation for nutraceuticals [346,348].

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 [252]. 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) [349]. 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) [251]. While promising, further animal and human studies are required to assess the therapeutic potential of these various nutraceuticals against COVID-19.

6.2.4.1 n-3 PUFA

Another potential nutraceutical that has exhibited beneficial effects against various viral infections is n-3 PUFA [349], such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA intake can come from a diet high in fish or through dietary supplementation with fish oils or purified oils [350].

Potential Mechanisms. n-3 PUFA nutraceuticals can mediate inflammation, and therefore they may have the capacity to modulate the adaptive immune response [342,350,351]. Another potential mechanism through which n-3 PUFA could exert beneficial effects against viral infections is by acting as precursor molecules for the biosynthesis of endogenous specialized proresolving mediators (SPM), such as protectins and resolvins, that actively resolve inflammation and infection [352]. Finally, some COVID-19 patients, particularly those with co-morbidities, are at a significant risk of thrombotic complications including arterial and venous thrombosis [119,353]. Therefore, the use of prophylactic and therapeutic anticoagulants and antithrombotic agents is under consideration [354].

Current Evidence. SPM have exhibited beneficial effects against a variety of lung infections including RNA viruses [355]. Indeed, protectin D1 has been shown to increase survival from H1N1 viral infection in mice by affecting the viral replication machinery [356]. Several mechanisms for SPM have been proposed, including preventing the release of pro-inflammatory cytokines and chemokines or increasing phagocytosis of cellular debris by macrophages [357]. In influenza, SPM promote antiviral B lymphocytic activities [358], and protectin D1 has been shown to increase survival from H1N1 viral infection in mice by affecting the viral replication machinery [356]. It is hypothesized that SPM may aid in the resolution of the cytokine storm and pulmonary inflammation associated with COVID-19 [359]. However, not all studies are in agreement that n-3 PUFA are effective against infections [360]. The effectiveness of n-3 PUFA against infections would be dependent on the dosage, timing, and the specific pathogens responsible [361]. On another level, there is still the question of whether fish oils can raise the levels of SPM levels upon ingestion and in response to acute inflammation in humans [362].

The increased risk of thrombotic complications in COVID-19 infected patients was reported relatively late in comparison to other COVID-19 manifestations [113,353]. Considering that there is significant

evidence that n-3 fatty acids and other fish oil-derived lipids possess antithrombotic properties and anti-inflammatory properties [363,364], they may have therapeutic value against the prothrombotic complications of COVID-19. Based on concern among the medical community that the use of investigational therapeutics on COVID-19 patients already on antiplatelet therapies due to a pre-existing comorbidities may lead to issues with dosing and drug choice, and/or negative drug-drug interactions [354], this supplementation may be particularly important for patients already receiving pharmaceutical antiplatelet therapies who may become infected. As a result, the use of other therapeutics such as dietary sources of n-3 fatty acids or nutraceuticals with antiplatelet activities may be beneficial and warrant further investigation. A new clinical trial [365] is currently recruiting COVID-19 positive patients to investigate the anti-inflammatory activity of a recently developed, highly purified derivative of EPA known as icosapent ethyl (VascepaTM) [366]. Other randomized controlled trials are in the preparatory stages with the intention of investigating the administration of EPA and other bioactive compounds to COVID-19 positive patients to determine whether anti-inflammatory effects or disease state improvements are observed [367,368]. Finally, while there have been studies investigating the therapeutic value of n-3 fatty acids against ARDS in humans, there is still limited evidence of their effectiveness [369].

Summary. The overall lack of human studies in this area means there is limited evidence as to whether these nutraceuticals could affect COVID-19 infection. Consequently, clinical trials that have been proposed and are in the preparatory stages will investigate the anti-inflammatory potential of n-3 PUFA and their derivatives for the treatment of COVID-19.

6.2.4.2 Zinc

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 [370]. Zinc supplements can be administered orally as a tablet or as a lozenge and they are available in many forms, such as 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 [370]. 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- κ B), thus altering cytokine production [371,372]. In particular, zinc supplementation can increase natural killer cell levels, which are important cells for host defense against viral infections [370,373].

Current Evidence. Adequate zinc intake has been associated with reduced incidence of infection [374] and antiviral immunity [375]. 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 [374]. 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 [376,377]. 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 [378,379]. Currently, there are over ten clinical trials registered with the intention to use zinc in a preventative or therapeutic manner. Many of these trials have proposed the use of zinc in conjunction with hydroxychloroquine and azithromycin [380,381,382,383]. However, it is not known how these trials will respond to the emerging lack of evidence supporting the use of hydroxychloroquine. Other trials are investigating zinc in conjunction with other nutrients such as vitamin C or n-3 PUFA [368,384].

Summary.

Though there is, overall, 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, the clinical trials that are currently underway will provide vital information on the efficacious use of zinc in COVID-19 prevention and/or treatment. However, given the limited risk, maintaining a healthy diet to ensure an adequate zinc status may be advisable for individuals seeking to reduce their likelihood of infection.

6.2.4.3 Vitamin C

Vitamins B, C, D, and E have also been suggested as potential nutrient supplement interventions for COVID-19 [349,385]. In particular vitamin C has been proposed as a potential 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 [386,387,388]. During viral infections vitamin C is utilized as evinced by lower concentrations in leukocytes and lower concentrations of urinary vitamin C. Post-infection, these levels return to baseline ranges [389,390,391,392,393].

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 [394]. Individual studies have found Vitamin C to reduce the susceptibility of patients to lower respiratory tract infections such as pneumonia [395]. Another 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%; $p = 0.001$) [396]. 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 [397]. Nevertheless, a randomized placebo-controlled trial [398] has begun in Wuhan, China to investigate the intravenous infusion of vitamin C to treat pneumonia in 140 severe COVID-19 infected patients. As summarized by Carr [399] the trial will not be completed until September 2020. Another trial in Italy [400] intends to deliver a 10 g infusion of vitamin C to 500 severe COVID-19 patients with pneumonia to assess in-hospital mortality over a 72 hr period as the primary outcome. The trial is currently recruiting and is due to run until March 2021. We will not know how effective vitamin C is as a therapeutic for quite some time due to the length of both trials. These are not the only trials investigating the potential value of vitamin C, as there are currently (as of June 2020) over fifteen trials registered with clinicaltrials.gov that are either recruiting or are currently in preparation. When completed, the trials will provide crucial evidence on the efficacy of vitamin C as a therapeutic for COVID-19 infection.

Summary. Some evidence suggests that vitamin C supplementation or infusion can shorten the duration of a cold, reduce an individual's susceptibility to infections, and shorten a patient's stay in an ICU when administered at high doses. We don't yet understand if these findings apply to COVID-19. There are ongoing trials in China and Italy that will inform our understanding of the therapeutic value of vitamin C supplementation for COVID-19.

6.2.4.4 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 biosynthesized by the body on exposure to sunlight.

Potential Mechanisms. Vitamin D deficiency is associated with an increased susceptibility to infection [401]. In particular, vitamin D deficient patients are at risk of developing acute respiratory infections [402] and ARDS [402]. 1,25-dihydroxyvitamin D3 (25-hydroxyvitamin D) 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 [401, 403]. Due to its potential immunomodulating properties, vitamin D supplementation may be advantageous to maintain a healthy immune system.

Current Evidence. A recent review postulated that an individual's vitamin D status may significantly affect their risk of developing COVID-19 [404]. This hypothesis was derived from the fact that the current pandemic emerged in winter in Wuhan China when 25-hydroxyvitamin D concentrations are at their lowest due to a lack of sunlight, whereas in the Southern Hemisphere, where it was nearing the end of the summer and higher 25-hydroxyvitamin D concentrations would be higher, the number of cases was low. 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 high-dose supplementation of vitamin D to treat infected patients and to prevent infection in hospital staff [404]. 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 affect COVID-19 outside of this geographic/climatic correlation. Likewise, though it is assumed that COVID-19 may be seasonal, multiple other factors that can affect vitamin D levels should also 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. As the pandemic evolves, further research has investigated some of the potential links identified in the Grant et al. review [404] between vitamin D and COVID-19 and sought to shed light on whether there is any prophylactic and/or therapeutic relationship. A study in Switzerland demonstrated that 27 SARS-CoV-2 positive patients exhibited 25-hydroxyvitamin D plasma concentrations that were significantly lower (11.1 ng/ml) than those of SARS-CoV-2 negative patients (24.6 ng/ml; $p = 0.004$), an association that held when stratifying for patients greater than 70 years old [405]. These findings seem to be supported by a Belgian observational study of 186 SARS-CoV-2 positive patients exhibiting symptoms of pneumonia, where 25-hydroxyvitamin D plasma concentrations were measured and a CT scan of the lungs was obtained upon hospitalization [406]. A significant difference in 25-hydroxyvitamin D levels was observed between the SARS-CoV-2 patients and 2,717 season-matched diseased controls. Both female and male patients possessed lower median 25-hydroxyvitamin D concentrations than the control group (18.6 ng/ml versus 21.5 ng/ml; $p = 0.0016$) and a higher rate of vitamin D deficiency (58.6% versus 42.5%). Evidence of sexual dimorphism was apparent, as female patients had equivalent levels of 23-hydroxyvitamin D to the control group, whereas male patients were deficient in 25-hydroxyvitamin D relative to male controls (67% versus 49%; $p = 0.0006$). Notably, vitamin D deficiency was progressively lower in males with advancing radiological disease stages ($p = 0.001$). Despite these two observational studies potentially linking vitamin D with COVID-19, an examination of the UK Biobank did not support this thesis [407]. This analysis examined 25-hydroxyvitamin D concentrations in 348,598 UK Biobank participants, of which 449 were SARS-CoV-2 positive. There is significant interest in the link between vitamin D and COVID-19, hence the multitude of studies published in the literature of varying quality and the clinical trials underway. One trial is currently investigating the utility of vitamin D as an immune-modulating agent by monitoring whether administration of vitamin D precipitates an improvement of health status in non-severe symptomatic patients infected with COVID-19 or whether vitamin D prevents patient deterioration [408]. Other trials are also underway examining various factors including mortality, symptom recovery, severity of disease, rates of ventilation, inflammatory markers such as

C-reactive protein (CRP) and IL-6, blood cell counts, and the prophylactic capacity of vitamin D administration [408,409,410,411]. Concomitant administration of vitamin D with pharmaceuticals such as aspirin [412] and bioactive molecules such as resveratrol [413] are also under investigation.

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.

6.2.4.5 Probiotics

Probiotics are "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [414]. Some studies suggest that probiotics are beneficial against common viral infections and there is modest evidence to suggest that they can modulate the immune response [415,416], as a result it has been hypothesized that probiotics may have therapeutic value worthy of investigation against SARS-CoV-2 [417].

Potential Mechanisms. Probiotics and next-generation probiotics, which are more akin to pharmacological-grade supplements, have been associated with multiple potential beneficial effects for allergies, digestive tract disorders, and even metabolic diseases through their anti-inflammatory and immunomodulatory effects [418,419]. However, the mechanisms by which probiotics affect these various conditions would likely differ among strains, with the ultimate effect of the probiotic depending on the heterogeneous set of bacteria present [419]. Some of the beneficial effects of probiotics include reducing inflammation by promoting the expression of anti-inflammatory mediators, inhibiting toll-like receptors (TLR) 2 and 4, direct competition with pathogens, the synthesis of antimicrobial substances or other metabolites, improving intestinal barrier function, and/or favorably altering the gut microbiota and the brain-gut axis [419,420,421]. However, there is also a bi-directional relationship between the lungs and gut microbiota known as the gut-lung axis [422], whereby gut microbial metabolites and endotoxins may affect the lungs via the circulatory system and the lung microbiota in return may affect the gut [423]. Therefore, the gut-lung axis may play role in our future understanding of COVID-19 pathogenesis and become a target for probiotic treatments [424].

Current Evidence. Probiotics have tentatively been associated with the reduction of risk and duration of viral upper respiratory tract infections [425,426,427]. Some meta-analyses that have assessed the efficacy of probiotics in viral respiratory infections have reported moderate reductions in the incidence and duration of infection [426,428]. Indeed, randomized controlled trials have shown that administering *Bacillus subtilis* and *Enterococcus faecalis* [429], *Lactobacillus rhamnosus* GG [430], or *Lactobacillus casei* and *Bifidobacterium breve* with galactooligosaccharides [431] via the nasogastric tube to ventilated patients reduced the occurrence of ventilator-associated pneumonia in comparison to the respective control groups in studies of viral infections and sepsis. These findings are supported by a recently published meta-analysis [432]. There is a significant risk of ventilator-associated bacterial pneumonia in COVID-19 patients [433], but it can be challenging for clinicians to diagnose this infection due to the fact that severe COVID-19 infection presents with the symptoms of pneumonia [434]. Therefore, an effective prophylactic therapy for ventilator-associated pneumonia in severe COVID-19 patients would be of significant therapeutic value.

Probiotics are generally synonymous with the treatment of gastrointestinal issues due to their supposed anti-inflammatory and immunomodulatory effects [435]. Notably, gastrointestinal symptoms commonly occur in COVID-19 patients [436], and the ACE2 receptor is highly expressed in enterocytes of the ileum and colon, suggesting that these organs may be a potential route of infection [437,438]. Indeed, SARS-CoV-2 viral RNA has been detected in human feces [439] and fecal-oral

transmission of the virus has not yet been ruled out [440]. Rectal swabs of some SARS-CoV-2 positive pediatric patients persistently tested positive for several days despite negative nasopharyngeal tests, indicating the potential for fecal viral shedding [441]. However, there is conflicting evidence for the therapeutic value of various probiotics against the incidence or severity of gastrointestinal symptoms in viral or bacterial infections such as gastroenteritis [442,443]. Nevertheless, it has been proposed that the administration of probiotics to COVID-19 patients and healthcare workers may prevent or ameliorate the gastrointestinal symptoms of COVID-19, a hypothesis that several clinical trials are now preparing to investigate [444,445]. Other studies are investigating whether probiotics may affect patient outcomes following SARS-CoV-2 infection [446].

Summary. Generally, the efficacy of probiotic use is a controversial topic among scientists. In Europe, EFSA has banned the term probiotics on products labels, which has elicited either criticism for EFSA or support for probiotics from researchers in the field [414,447,448]. This is due to the hyperbolic claims placed on the labels of various probiotic products, which lack rigorous scientific data to support their efficacy. Overall, the data supporting probiotics in the treatment or prevention of many different disorders and diseases is not conclusive as the quality of the evidence is generally considered low [425]. However, in the case of probiotics and respiratory infections, the evidence seems to be supportive of their potential therapeutic value. Consequently, several investigations are underway to investigate the prophylactic and therapeutic potential of probiotics for COVID-19. However, blind use of conventional probiotics for COVID-19 is cautioned against until the pathogenesis of SARS-CoV-2 is further established [449]. Until clinical trials investigating the prophylactic and therapeutic potential of probiotics for COVID-19 are complete, it is not possible to provide an evidence-based recommendation for their use.

6.2.4.6 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 [450,451]. Nutritional strategies and the use of nutraceuticals will also undoubtedly play a role in the treatment of hospitalized patients as malnutrition is a risk to COVID-19 patients [452]. 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. As a result, the administration of zinc, vitamin C, and vitamin D in conjunction with hydroxychloroquine are being investigated for their prophylactic effects in healthcare workers and their first-degree relatives in Turkey [453]. However, many supplements and nutraceuticals designed for various ailments are available in the United States and beyond that are not strictly regulated [454]. Indeed, there can be safety and efficacy concerns associated with many of these products. Often, the vulnerable members 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 [455]. 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 and because they are currently under clinical investigation. Therefore, further intensive investigation is required to establish the effects of these nutraceuticals, if any, against COVID-19. Until effective therapeutics are established, the most effective mitigation strategies consist of encouraging standard public health practices such as regular hand washing with soap, wearing a face mask, and covering a cough with your elbow [456], along with following social distancing measures, "stay in place" guidelines, expansive testing, and contact tracing [457,458].

6.3 Biologics

Biologics are produced from components of living organisms or viruses. They include antibodies such as the humanized monoclonal antibody (mAb) tocilizumab (TCZ), neutralizing antibodies (nAbs), and vaccines.

6.3.1 Tocilizumab

TCZ is a receptor antibody that was developed to manage chronic inflammation caused by the continuous synthesis of the cytokine interleukin-6 (IL-6) [459]. IL-6 is a pro-inflammatory cytokine belonging to the interleukin family, immune system regulators that are primarily responsible for immune cell differentiation. Often used to treat conditions such as rheumatoid arthritis [459], TCZ has become a pharmaceutical of interest for the treatment of COVID-19. While secretion of IL-6 can be associated with chronic conditions, it is a key player in the innate immune response that is secreted by macrophages in response to the detection of PAMPs or DAMPs [459]. An analysis of 191 in-patients at two Wuhan hospitals revealed that blood concentrations of IL-6 differed between patients who did and did not recover from COVID-19. Patients who ultimately deceased had higher IL-6 levels at admission than those who recovered [98]. Additionally, IL-6 levels remained higher throughout the course of hospitalization in the patients who ultimately deceased [98]. This finding provided some early evidence that COVID-19 deaths may be induced by the hyperactive immune response, which can be either the cytokine release syndrome (CRS) or cytokine storm syndrome (CSS), as IL-6 plays a key role in this response [460]. In this context, the observation of elevated IL-6 in patients who died may reflect an over-production of proinflammatory interleukins, suggesting that TCZ may palliate some of the most severe symptoms of COVID-19 associated with increased cytokine production.

6.3.1.1 Anticipated Mechanism

Human IL-6 is a 26-kDa glycoprotein that consists of 184 amino acids and contains two potential N-glycosylation sites and four cysteine residues. It binds to a type I cytokine receptor (IL-6R α or glycoprotein 80) that exists in both membrane-bound (IL-6R α) and soluble (sIL-6R α) forms [461]. It is not the binding of IL-6 to the receptor that initiates pro- and/or anti-inflammatory signaling, but rather the binding of the complex to another subunit, known as IL-6R β or glycoprotein 130 (gp130) [461,462]. Unlike membrane-bound IL-6R α , which is only found on hepatocytes and some types of leukocytes, gp130 is found on most cells [463]. When IL-6 binds to sIL-6R α , the complex can then bind to a gp130 protein on any cell [463]. The binding of IL-6 to IL-6R α is termed classical signaling, while its binding to sIL-6R α is termed trans-signaling [463,464,465]. These two signaling processes are thought to play different roles in health and illness. For example, trans-signaling may play a role in the proliferation of mucosal T-helper TH2 cells associated with asthma, while an earlier step in this proliferation of process may be regulated by classical signaling [463]. Similarly, IL-6 is known to play a role in Crohn's Disease via trans-, but not classical, signaling [463]. Both classical and trans-signaling can occur through three 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 [461]. These signaling pathways are involved in a variety of different functions, including cell type differentiation, immunoglobulin synthesis, and cellular survival signaling pathways, respectively [461]. The ultimate result of the IL-6 cascade is to direct transcriptional activity of various promoters of pro-inflammatory cytokines, such as IL-1, TFN, and even IL-6 itself, through the activity of NF- κ B [461]. IL-6 synthesis is tightly regulated both transcriptionally and post-transcriptionally, and it has been shown that viral proteins can enhance transcription of the IL-6 gene by strengthening the DNA-binding activity between several transcription factors and IL-6 gene-cis-regulatory elements [466]. Therefore, drugs inhibiting the binding of IL-6 to IL-6R α or sIL-6R α are of interest for combating the hyperactive inflammatory response characteristic of CRS and CSS. TCZ is a humanized monoclonal antibody that binds both to the insoluble and soluble receptor of IL-6, providing de facto inhibition of the IL-6 immune cascade.

Current Evidence. Tocilizumab is being administered either as an intervention or as concomitant medication in 74 COVID-19 clinical trials (Figure 3). No randomized, placebo-controlled studies have been released yet for TCZ. Therefore, no conclusions can be drawn about its efficacy for the treatment of COVID-19. However, early interest in TCZ as a possible treatment for COVID-19 emerged from a very small retrospective study in China that examined 20 patients with severe symptoms in early February 2020 and reported rapid improvement in symptoms following treatment with TCZ [467]. Subsequently, a number of retrospective studies have been conducted in several countries. Many studies use a retrospective, observational design, where they compare outcomes for COVID-19 patients who received TCZ to those who did not over a set period of time. For example, one of the largest retrospective, observational analysis released to date [468] compared the rates at which patients who received TCZ deceased or progressed to invasive medical ventilation over a 14-day period compared to patients receiving only SOC.

Under this definition, SOC could include other drugs such as HCQ, azithromycin, lopinavir-ritonavir or darunavir-cobicistat, or heparin. While this study was not randomized, a subset of patients who were eligible to receive TCZ were unable to obtain it due to shortages; however, these groups were not directly compared in the analysis. After adjusting for variables such as age, sex, and SOFA score, they found that patients treated with TCZ were less likely to progress to invasive medical ventilation and/or death (adjusted hazard ratio = 0.61, CI 0.40-0.92, $p=0.020$), although analysis of death and ventilation separately suggests that this effect may have been driven by differences in the death rate (20% of control versus 7% of TCZ-treated patients). They reported particular benefits for patients whose $\text{PaO}_2/\text{FiO}_2$ (P/F) ratio, also known as the Horowitz Index for Lung Function, fell below a 150 mm Hg threshold. They found no differences between groups administered subcutaneous versus intravenous TCZ. Another retrospective observational analysis of interest examined the charts of patients at a hospital in Connecticut, USA where 64% of all 239 COVID-19 patients in the study period were administered TCZ based on assignment by a standardized algorithm [469]. They found that TCZ administration was associated with more similar rates of survivorship in patients with severe versus nonsevere COVID-19 at intake, defined based on the amount of supplemental oxygen needed. They therefore proposed that their algorithm was able to identify patients presenting with or likely to develop CRS as good candidates for TCZ. They also reported higher survivorship in Black and Hispanic patients compared to white patients when adjusted for age. The major limitation with interpretation for these studies is that there may be clinical characteristics that influenced medical practitioners decisions to administer TCZ to some patients and not others. One interesting example therefore comes from an analysis of patients at a single hospital in Brescia, Italy, where TCZ was not available for a period of time [470]. This study compared COVID-19 patients admitted to the hospital before and after March 13, 2020, when the hospital received TCZ. Therefore, patients who would have been eligible for TCZ prior to this arbitrary date did not receive it as treatment, making this retrospective analysis something of a natural experiment. Despite this design, demographic factors did not appear to be consistent between the two groups, and the average age of the control group was older than the TCZ group. The control group also had a higher percentage of males and a higher incidence of comorbidities such as diabetes and heart disease. All the same, the multivariate hazard ratio, which adjusted for these clinical and demographic factors, found a significant difference between survival in the two groups ($\text{HR}=0.035$, $\text{CI}=0.004\text{-}0.347$, $p = 0.004$). They reported improvement of survival outcomes after the addition of TCZ to their SOC regime, with 11 of 23 patients (47.8%) admitted prior to March 13th dying compared to 2 of 62 (3.2%) admitted afterwards. They also reported a reduced progression to mechanical ventilation in the TCZ group. However, this study also holds a significant limitation: the time delay between the two groups means that knowledge about how to treat the disease likely improved over this timeframe as well. All the same, the results of these observational retrospective studies provide support for TCZ as a pharmaceutical of interest for follow-up in clinical trials.

In addition to the retrospective observational studies, other analysis have utilized a retrospective case-control design to match pairs of patients with similar baseline characteristics, only one of whom

received TCZ for COVID-19. In one such study, TCZ was significantly associated with a reduced risk of progression to ICU admission or death [471]. This study examined only 20 patients treated with TCZ compared (all but one of the patients treated with TCZ in the hospital during the study period) to 25 patients receiving standard of care. For the combined primary endpoint of death and/or ICU admission, only 25% of patients receiving TCZ progressed to an endpoint compared to 72% in the SOC group ($p = 0.002$ presumably based on a chi-square test). When the two endpoints were examined separately, progression to invasive medical ventilation remained significant (32% SOC compared to 0% TCZ, $p = 0.006$) but not for mortality (48% SOC compared to 25% TCZ, $p = 0.066$). In contrast, a study that compared 96 patients treated with TCZ to 97 patients treated with SOC only in New York City found that differences in mortality did not differ between the two groups, but that this difference did become significant when intubated patients were excluded from the analysis [472]. Taken together, these findings suggest that future clinical trials of TCZ may want to include intubation as an endpoint. However, these studies should be approached with caution, not only because of the small number of patients enrolled and retrospective design, but also because they performed a large number of statistical tests and did not account for multiple hypothesis testing. These last findings highlight the need to search for a balance between impairing a harmful immune response, such as the one generated during CRS and CSS, and preventing the worsening of the clinical picture of the patients by potential new viral infections.

Though data about TCZ for COVID-19 is still only just emerging, some meta-analyses and systematic reviews have investigated the available data. One meta-analysis [473] evaluated 19 studies published or released as preprints prior to July 1, 2020 and found that the overall trends supportive of the frequent conclusion that TCZ does improve survivorship, with a significant hazard ratio of 0.41. This trend improved when they excluded studies that administered a steroid alongside TCZ, with a significant hazard ratio of 0.04. They also found some evidence for reduced IMV or ICU admission, but only when excluding all studies except a small number reporting estimates that were adjusted for possible bias introduced by the challenges of stringency during the enrollment process. A systematic analysis of nine case-control studies estimated a hazard ratio of 0.482, which was also significant [474]. Although these estimates are similar, it is important to note that they are drawing from the same literature and are therefore likely to be affected by the same biases in publication. A second systematic review of studies investigating TCZ treatment for COVID-19 analyzed 31 studies that had been published or released as pre-prints and reported that none carried a low risk of bias (RoB) [475]. Therefore, the present evidence is not likely to be sufficient for conclusions about the efficacy of TCZ.

Safety. TCZ has been used for over a decade to treat RA [476], and a recent study shows that the drug is safe for pregnant and breastfeeding women [477]. However, TCZ may increase the risk of developing infections [10.1177/1759720X18798462], and RA patients with chronic hepatitis B (HB) infections had a high risk of HB virus reactivation when TCZ was administered in combination with other RA drugs [478]. As a result, TCZ is contraindicated in patients with active infections such as tuberculosis [479]. Previous studies have investigated, with varying results, a possible increased risk of infection in RA patients administered TCZ [480,481], although another study reported that the incidence rate of infections was higher in clinical practice RA patients treated with TCZ than in the rates reported by clinical trials [482]. In the investigation of 544 Italian COVID-19 patients, the group treated with TCZ was found to be more likely to develop secondary infections, with 24% compared to 4% in the control group [???]. Reactivation of hepatitis B and herpes simplex virus 1 was also reported in a small number of patients in this study, all of whom were receiving TCZ. A July 2020 case report described negative outcomes of two COVID-19 patients after receiving TCZ, including one death; however, both patients were intubated and had entered septic shock prior to receiving TCZ [???], likely indicating a severe level of cytokine production. Additionally, D-dimer and sIL2R levels were reported by one study to increase in patients treated with TCZ, which raised concerns because of the potential association between elevated D-dimer levels and thrombosis and between sIL2R and diseases where T-cell regulation is compromised [469]. An increased risk of bacterial infection was also identified in a systematic review of the literature, based on the unadjusted estimates reported [473]. In summary,

TCZ administration to COVID-19 patients is not without risks, may introduce additional risk of developing secondary infections, and should be approached especially cautiously for patients who have latent viral infections.

Summary. Approximately 25% of coronavirus patients develop ARDS, which is caused by an excessive early response of the immune system which can be a component of cytokine release syndrome [469] and cytokine storm syndrome [479]. This overwhelming inflammation is triggered by IL-6. TCZ is an inhibitor of IL-6 and therefore may be able to neutralize the inflammatory pathway that leads to the cytokine storm. While the mechanism suggests TCZ may be beneficial for the treatment of COVID-19 patients experiencing excessive immune activity, no randomized controlled trials are available assessing its effect. However, small initial studies have found preliminary indications that TCZ may reduce progression to invasive medical ventilation and/or death. It should be noted that SOC varied widely across retrospective studies, with one study administering HCQ, lopinavir-ritonavir, antibiotics, and/or heparin as part of standard care. Interest in TCZ as a treatment for COVID-19 was supported by two meta-analyses that converged on a hazard ratio estimate of approximately 0.45 [473,474], but a third meta-analysis found that all of the available literature carries a risk of bias, with even the largest available TCZ studies to date carrying a moderate risk of bias under the ROBINS-I criteria [475]. Additionally, different studies used different dosages, number of doses, and methods of administration; ongoing research may be needed to optimize administration of TCZ [483], although similar results were reported by one study for intravenous and subcutaneous administration [???]. Clinical trials that are in progress are likely to provide additional insight into the effectiveness of this drug for the treatment of COVID-19 along with how it should be administered.

6.3.2 Neutralizing Antibodies

Monoclonal antibodies 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 [484]. There are currently 79 FDA approved mAbs on the market including antibodies for viral infections (e.g. Ibalizumab for HIV and Palivizumab for RSV) [484,485]. 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 [486,487]. 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.

6.3.2.1 Spike (S) Neutralizing Antibody

During the first SARS epidemic in 2002, nAbs were found in SARS-CoV infected patients [488,489]. Several studies following up on these findings identified various S glycoprotein epitopes as the major targets of neutralizing antibodies against SARS-CoV [490]. 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 [491]. Similarly, a meta-analysis suggested that administration of plasma from recovered SARS-CoV patients reduced mortality upon SARS-CoV infection [492].

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 [493; doi:10.1128/JVI.00912-14].

Anticipated Mechanisms. Coronaviruses use trimeric spike (S) glycoproteins on their surface to bind to host cell receptors, such as ACE2, allowing for cell entry [44,46]. 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 [490]. Although targeting of the host cell receptor ACE2 shows efficacy in inhibiting SARS-CoV-2 infection [62], given the physiological relevance of ACE2 [494], 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.

Current Evidence. The first human neutralizing antibody against SARS-CoV-2 targeting the trimeric spike (S) glycoproteins has been developed using hybridoma technology, [495], 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 [495,496]. 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 [497]. 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 [136]. Interestingly, the patient isolated antibodies did not cross-react with RBDs 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 [498,499]. 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 [500]. For MERS-CoV, a combination of multiple neutralizing antibodies targeting different antigenic sites prevented neutralization escape [501]. 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 [136]. 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 [502].

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 [501]. 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 [502]. These findings underscores our current lack of understanding the full immune response to SARS-CoV-2.

6.3.3 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 [460]. Specifically, IFNs I (IFN- α and β) and II (IFN- γ) induce the

expression of antiviral proteins that bring the viral RNA to degradation [503]. Among these IFNs, IFN- β has already been found to strongly inhibit the replication of other coronaviruses, such as SARS-CoV, in cell culture, while IFN- α and γ were shown to be less effective in this context [503]. There is evidence that patients with higher susceptibility to ARDS indeed show deficiency in IFN- β . For instance, infection with other coronaviruses impairs IFN- β expression and synthesis, allowing the virus to escape the innate immune response [504].

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 the 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.

6.3.4 Vaccines

6.3.4.1 Strategies for and challenges to vaccine development

Today, the first step in producing a vaccine often is characterizing the target. The genetic sequence of SARS-CoV-2 was published on January 11, 2020, which aided the global effort to develop a vaccine to prevent COVID-19. The Coalition for Epidemic Preparedness Innovations (CEPI) is coordinating global health agencies and pharmaceutical companies to develop vaccines against SARS-CoV-2. As of April 8, 2020, there were 115 vaccine candidates to prevent COVID-19, of which 78 were active. Of the 78 active vaccine programs, 73 were in the preclinical or exploratory stage [505].

Historically, an H1N1 influenza vaccine was developed relatively efficiently, mainly because influenza-vaccine technology had already been developed and regulatory agencies had already decided that vaccines produced using egg- and cell-based platforms could be licensed under the regulations used for a strain change. Critiques of the experience producing and distributing the H1N1 vaccine have stressed the need for alternative development-and-manufacturing platforms that can be readily adapted to new pathogens. Although a monovalent H1N1 vaccine was not available before the pandemic peaked in the United States and Europe, it was available soon afterward as a stand-alone vaccine that was eventually incorporated into the commercially available seasonal influenza vaccines [506]. If H1N1 vaccine development provides any indication, considering developing and manufacturing platforms for promising COVID-19 vaccine trials early could hasten the emergence of an effective prophylactic vaccine against SARS-CoV-2.

Unlike many global vaccine development programs previously, such as with H1N1, the vaccine development landscape for COVID-19 includes vaccines produced by a wide array of technologies. Experience in the field of oncology is encouraging COVID-19 vaccine developers to use next-generation approaches to vaccine development, which have led to the great diversity of vaccine development programs [507]. Diverse technology platforms include DNA, RNA, virus-like particle, recombinant protein, both replicating and non-replicating viral vectors, live attenuated virus, and inactivated virus approaches. Given the wide range of vaccines under development, it is possible that some vaccine products may eventually be shown to be more effective in certain subpopulations, such as children, pregnant women, immunocompromised patients, the elderly, etc. The requirements for a

successful vaccine trial and deployment are complex and may require coordination between government, industry, academia, and philanthropic entities [508]. While little is currently known about immunity to SARS-CoV-2, vaccine development typically tests for serum neutralizing activity, as this has been established as a biomarker for adaptive immunity in other respiratory illnesses [509].

6.3.4.1.1 DNA Vaccines

This vaccination method involves the direct introduction of a plasmid containing a DNA sequence encoding the antigen(s) against which an immune response is sought into appropriate tissues [510].

Anticipated Mechanism. This approach may offer several advantages over traditional vaccination approaches, such as the stimulation of both B- as well as T-cell responses and the absence of any infectious agent.

Current Evidence. Currently, a Phase I safety and immunogenicity clinical trial of INO-4800, a prophylactic vaccine against SARS-CoV-2, is underway [511]. The vaccine developer Inovio Pharmaceuticals Technology is overseeing administration of INO-4800 by intradermal injection followed by electroporation with the CELLECTRA® device to healthy volunteers. Electroporation is the application of brief electric pulses to tissues in order to permeabilize cell membranes in a transient and reversible manner. It has been shown that electroporation can enhance vaccine efficacy by up to 100-fold, as measured by increases in antigen-specific antibody titers [512]. The safety of the CELLECTRA® device has been studied for over seven years, and these studies support the further development of electroporation as a safe vaccine delivery method [513]. The temporary formation of pores through electroporation facilitates the successful transportation of macromolecules into cells, allowing cells to robustly take up INO-4800 for the production of an antibody response.

Approved by the U.S. Food and Drug Administration (FDA) on April 6, 2020, the Phase I study is enrolling up to 40 healthy adult volunteers in Philadelphia, PA at the Perelman School of Medicine and at the Center for Pharmaceutical Research in Kansas City, MO. The trial has two experimental arms corresponding to the two locations. Participants in Experimental Group 1 will receive one intradermal injection of 1.0 milligram (mg) of INO-4800 followed by electroporation using the CELLECTRA® 2000 device twice, administered at Day 0 and Week 4. Participants in Experimental Group 2 will receive two intradermal injections of 1.0 mg (total 2.0 mg per dosing visit) of INO-4800 followed by electroporation using the CELLECTRA® 2000 device, administered at Day 0 and Week 4. Safety data and the initial immune responses of participants from the trial are expected by the end of the summer of 2020.

Summary. The development of a DNA vaccine against SARS-CoV-2 by Inovio could be an important step forward in the world's search for a COVID-19 vaccine. Although exciting, the cost of vaccine manufacturing and electroporation may make scaling the use of this technology for prophylactic use for the general public difficult.

6.3.4.1.2 RNA Vaccines

RNA vaccines are nucleic-acid based modalities that code for viral antigens against which the human body elicits a humoral and cellular immune response. The mRNA technology is transcribed *in vitro* and delivered to cells via lipid nanoparticles (LNP) [514]. They are recognized by ribosomes *in vivo* and then translated and modified into functional proteins [515]. The resulting intracellular viral proteins are displayed on surface MHC proteins, provoking a strong CD8+ T cell response as well as a CD4+ T cell and B cell-associated antibody responses [515].

Naturally, mRNA is not very stable and can degrade quickly in the extracellular environment or the cytoplasm. The LNP covering protects the mRNA from enzymatic degradation outside of the cell [516]. Codon optimization to prevent secondary structure formation and modifications of the poly-A tail as

well as the 5' untranslated region to promote ribosomal complex binding can increase mRNA expression in cells. Furthermore, purifying out dsRNA and immature RNA with FPLC (fast performance liquid chromatography) and HPLC (high performance liquid chromatography) technology will improve translation of the mRNA in the cell [515,517].

Vaccines based on mRNA delivery confer many advantages over traditional viral vectored vaccines and DNA vaccines. In comparison to live attenuated viruses, mRNA vaccines are non-infectious and can be synthetically produced in an egg-free, cell-free environment, thereby reducing the risk of a detrimental immune response in the host [518]. Unlike DNA vaccines, mRNA technologies are naturally degradable and non-integrating, and they do not need to cross the nuclear membrane in addition to the plasma membrane for their effects to be seen [515]. Furthermore, mRNA vaccines are easily, affordably, and rapidly scalable.

Although mRNA vaccines have been developed for therapeutic and prophylactic purposes, none have been licensed or commercialized thus far. Nevertheless, they have shown promise in animal models and preliminary clinical trials for several indications, including rabies, coronavirus, influenza, and cytomegalovirus [519]. Preclinical data from Pardi et al. identified effective antibody generation against full-length FPLC-purified influenza hemagglutinin stalk-encoding mRNA in mice, rabbits, and ferrets [520]. Similar immunological responses for mRNA vaccines were observed in humans in Phase I and II clinical trials operated by the pharmaceutical-development companies Curevac and Moderna for rabies, flu, and zika [517].

Anticipated Mechanism. Positively charged bilayer LNPs carrying the mRNA attract negatively charged cell membranes, endocytose into the cytoplasm [516], and facilitate endosomal escape. LNPs can be coated with modalities recognized and engulfed by specific cell types. LNPs 150nm or less effectively enter into lymphatic vessels.

There are three types of RNA vaccines: non-replicating, *in vivo* self-replicating, and *in vitro* dendritic cell non-replicating [521]. Non-replicating mRNA vaccines consist of a simple open reading frame (ORF) for the viral antigen flanked by the 5' UTR and 3' poly-A tail. *In vivo* self-replicating vaccines encode a modified viral genome derived from single-stranded, positive sense RNA alphaviruses [515,517]. The RNA genome encodes the viral antigen along with proteins of the genome replication machinery, including an RNA polymerase. Structural proteins required for viral assembly are not included in the engineered genome [515]. Self-replicating vaccines produce more viral antigens over a longer period of time, thereby evoking a more robust immune response [521]. Finally, *in vitro* dendritic cell non-replicating RNA vaccines limit transfection to dendritic cells. Dendritic cells are potent antigen-presenting immune cells that easily take up mRNA and present fragments of the translated peptide on their MHC proteins, which can then interact with T cell receptors. Ultimately, primed T follicular helper cells can stimulate germinal center B cells that also present the viral antigen to produce antibodies against the virus [522]. These cells are isolated from the patient, grown and transfected *ex vivo*, and reintroduced to the patient [523].

Current Evidence. mRNA-1273 was the first COVID-19 vaccine to enter a phase I clinical in the United States. ModernaTX, Inc. is currently spearheading an investigation on the immunogenicity and reactogenicity of mRNA-1273, a conventional lipid nanoparticle encapsulated RNA encoding a full-length prefusion stabilized spike (S) protein for SARS-CoV-2 [524]. In a study that is ongoing, forty-five participants were enrolled and given intramuscular injections of mRNA-1273 in their deltoid muscle on day 1 and day 29, and then followed for the next twelve months. Healthy males and non-pregnant females aged 18-55 years were recruited for this study and divided into three groups receiving 25, 100, or 250 micrograms (µg) of mRNA-1273. IgG ELISA assays on patient serology samples are being used to examine the immunogenicity of the vaccine [524].

A preliminary report describing initial safety and immunogenicity findings is now available [\[509\]](#). Binding antibodies were observed at two weeks after the first dose at all concentrations. At the time point one week after the second dose was administered on day 29, the pseudotyped lentivirus reporter single-round-of-infection neutralization assay (PsVNA), which was used to assess neutralizing activity, reached a median level similar to the median observed in convalescent plasma samples. Participants reported mild and moderate systemic adverse events after the day 1 injection, and one severe local event was observed in each of the two highest dose levels. The second injection led to severe systemic adverse events for three of the participants at the highest dose levels, with one participant in the group being evaluated at an urgent care center on the day after the second dose. The reported localized adverse events from the second dose were similar to those from the first.

Summary. mRNA vaccines are promising tools in the prevention and control of pandemics because they may sidestep many challenges associated with traditional vaccine design and manufacturing. mRNA-1273 is the only RNA vaccine for SARS-CoV-2 for which preliminary results are available. This early in the development process, placebo-blinded and randomized results are not yet available, but the initial results are promising. In the dose ranging study, even the lowest dose of 25 µg of mRNA-1273 appeared to be sufficient to induce an immunogenicity profile comparable to that observed in convalescent plasma and appeared to be well tolerated among the population of healthy, non-pregnant participants from 18-55 years of age. Based on the preliminary results from mRNA-1273 [\[509\]](#), a new trial aims to enroll 30,000 participants who will be randomized for two injections of 100 µg of mRNA-1273 or placebo, again spaced 28 days apart [\[525\]](#).

6.3.4.1.3 Viral Particle Vaccines

Brief background on the therapeutic.

6.3.4.2 Oligonucleotide Therapies

Add background and other information below

6.3.4.3 Adjuvants for Vaccines

Adjuvants include a variety of molecules or larger microbial-related products which sometimes are or include immunostimulants or immunomodulators or more generally have an effect on the immune system or immune responses of interest. Adjuvants are sometimes included within vaccines, especially vaccines other than live attenuated and inactivated viruses, in order to enhance the immune response. A review on the development of SARS-CoV-2 vaccines [\[526\]](#) also included a brief summary of considerations for adjuvants to research for the vaccines including a brief description of some already commonly used adjuvants. Different adjuvants can regulate different types of immune responses, so the type of adjuvant or combination of adjuvants for use in a vaccine depends on the type of vaccine and the research into what works with respect to efficacy and safety. A variety of possible mechanisms for adjuvants have been researched [\[527, 528, 529\]](#) including the following: induction of DAMPs (damage-associated molecular patterns) which can be recognized by certain pattern recognition receptors (PRRs) of the innate immune system; being or including or functioning as PAMPs (pathogen-associated molecular patterns) which can also be recognized by certain pattern recognition receptors (PRRs); and more generally enhancing humoral or cellular immune responses. When choosing an adjuvant or combination of adjuvants, considerations include promotion of advantageous effects of the components and immune response and avoiding or inhibition of possible deleterious effects of the components and immune response. There are also considerations, technologies, and research into the effects of different ways to deliver (or co-deliver or combine) the adjuvant and antigen components of a vaccine.

6.4 Underexplored Therapeutics

The majority of current clinical trials and lines of investigation have focused on repurposing existing therapies to counter SARS-CoV-2 and treat its symptoms. This is necessary given the urgency of the situation as well as the extensive time required for developing and testing new therapies. However, in the long-term, new drugs specific for treatment of COVID-19 may also enter development. There is thus value in investigating two lines of inquiry for treatment of COVID-19: 1) new therapeutics specific for treatment of COVID-19 or its symptoms, and 2) repurposing of existing therapeutics for treatment of COVID-19 or its symptoms. Here we consider further avenues that scientific investigators may explore in the development of therapies for COVID-19.

Given the great focus in investigating hydroxychloroquine (HCQ) as a potential antiviral treatment for SARS-CoV-2, it may be of interest to researchers to explore related alternatives. For example, hydroxyferroquine derivatives of HCQ have been described as a class of bioorganometallic compounds that exert antiviral effects with some selectivity for SARS-CoV [530]. Future work could explore whether these compounds exert antiviral effects against SARS-CoV-2 and whether they are safe for use in animals and humans.

The tocilizumab trial described in an above section [98] studies the possibility of using an anti-inflammatory agent typically used for the treatment of autoimmune disease to counter the effects of the “cytokine storm” induced by the virus. Another anti-IL-6 antibody, sarilumab, is also being investigated [531,532]. Typically, immunosuppressive drugs such as these are contraindicated in the setting of infection [533]. However, COVID-19 results in hyperinflammation that appears to contribute to mortality via lung damage, suggesting that immunosuppression may be a helpful approach to treatment [77]. The decision of whether and/or when to counter hyperinflammation with immunosuppression in the setting of COVID-19 remains in debate as the risks of inhibiting antiviral immunity continue to be weighed against the beneficial anti-inflammatory effects [534]. If the need to curtail the “cytokine storm” inflammatory response to the virus transcends the risks of immunosuppression, exploration of more anti-inflammatory agents may be warranted; these agents are considered here. While tocilizumab targets IL-6, several other inflammatory markers could be potential targets, including TNF-alpha. Inhibition of TNF-alpha by an inhibitor such as Etanercept has been previously suggested for treatment of SARS-CoV [535] and may be relevant for SARS-CoV-2 as well. Baricitinib and other small molecule inhibitors of the JAK kinase pathway also curtail the inflammatory response and have been suggested as potential options for SARS-CoV-2 infections [536]. Baricitinib in particular may be able to reduce the ability of SARS-CoV-2 to infect lung cells [537]. Clinical trials studying baricitinib in COVID-19 have already begun in the US and in Italy [538,539]. Identification and targeting of further inflammatory markers that are relevant in SARS-CoV-2 infection may be of value for curtailing the inflammatory response and lung damage. Lastly, it is also worth noting the high costs of tocilizumab therapy and other biologics: at doses used for rheumatoid arthritis patients, the cost for tocilizumab ranges from \$179.20 to \$896 per dose for the IV form and \$355 for the pre-filled syringe [540]. Cyclosporine may be a more cost-effective and readily-available alternative than biologics [541], if it proves effective against the cytokine storm induced by SARS-CoV-2.

Another approach is the development of antivirals, which could be broad-spectrum, specific to coronaviruses, or targeted to SARS-CoV-2. Given the increasingly apparent role of the cytokine storm in disease pathogenesis, it is possible that antivirals could be less effective in more severe cases of COVID-19, but this is not yet known; regardless, it is likely that early-stage patients could benefit from antiviral therapy. The potential for remdesivir as an antiviral has already been described in an above section. Development of new antivirals is complicated by the fact that none have yet been approved for human coronaviruses. Intriguing new options are emerging, however. Beta-D-N4-hydroxycytidine (NHC) is an orally bioavailable ribonucleotide analog showing broad-spectrum activity against RNA viruses, which may inhibit SARS-CoV-2 replication [542]. Various other antivirals are in development. Development of antivirals will be further facilitated as research reveals more information about the interaction of SARS-CoV-2 with the host cell and host cell genome, mechanisms of viral replication,

mechanisms of viral assembly, and mechanisms of viral release to other cells; this can allow researchers to target specific stages and structures of the viral life cycle.

Antibodies against viruses, also known as antiviral monoclonal antibodies, could be an alternative as well and are described in detail in an above section. The goal of antiviral antibodies is to neutralize viruses through either cell-killing activity or blocking of viral replication [543]. They may also engage the host immune response, encouraging the immune system to hone in on the virus. Given the cytokine storm that results from immune system activation in response to the virus, which has been implicated in worsening of the disease, a neutralizing antibody (nAb) may be preferable. Upcoming work may explore the specificity of nAbs for their target, mechanisms by which the nAbs impede the virus, and improvements to antibody structure that may enhance the ability of the antibody to block viral activity.

There is also some research into possible potential therapeutics or prophylactics which interact with components of the innate immune response. For example, there are a variety of toll-like receptors (TLRs) which are examples of pattern recognition receptors (PRRs), innate immune response components which recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Note that TLRs form a part of innate immune recognition and can more generally contribute to promoting both innate and adaptive responses [86]. In mouse models, poly(I:C) and CpG, which are agonists of toll-like receptors TLR3 and TLR9, respectively, showed protective effects when administered prior to SARS-CoV infection [544]. Therefore, TLR agonists hold some potential for broad-spectrum prophylaxis. Another type of approach which is being investigated is the possible use of what is termed trained immunity, in particular as elicited by non-SARS-CoV-2 whole-microorganism vaccines (or other microbial stimuli), as a tool which might be shown to generate heterologous protective effects with respect to SARS-CoV-2 susceptibility or severity [545]. In a recent review [546], trained immunity was defined as forms of memory which are temporary (e.g., months or years, and reversible), displayed by innate immune cells and innate immune features of other cells, displayed as increased responsiveness to future same or heterologous pathogen infection or sometimes decreased responsiveness or immunological tolerance, and established through epigenetic and metabolic mechanisms. One type of stimulus which research indicates can induce trained immunity is bacillus Calmette-Guerin (BCG) vaccination. BCG is an attenuated form of bacteria *Mycobacterium bovis*. The vaccine is most commonly administered for the prevention of tuberculosis in humans. With respect to SARS-CoV-2 specifically, clinical trials in non-SARS-CoV-2-infected adults have been setup to assess the possible efficacy of BCG vaccination – e.g., to assess if it may be effective as a potential prophylactic or potential partial prophylactic in (1) reducing susceptibility / preventing infection and (2) reducing disease severity (for descriptions of trials with BCG vaccine or the related vaccine VPM1002, see [545, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560]). Some trials enroll healthcare workers, other trials hospitalized elderly adults without immunosuppression who get vaccinated with placebo or BCG at hospital discharge, and yet another set of trials older adults (>50 years) under chronic care for conditions like hypertension and diabetes. One set of trials, for example, uses time until first infection as the primary study endpoint; more generally, outcomes measured in some of these trials are related to incidence of disease and disease severity or symptoms. An article [545] that very briefly summarizes the setup of these trials also mentions some data analyses which showed possible correlations between countries which have more BCG vaccination (or BCG vaccination policies) and the severity of COVID-19 in those countries, but (1) it is unclear whether this correlation indicates an interaction because for example of many other possible factors or confounding factors (country age distribution, detection efficiency, stochastic epidemic dynamic effects, differences in healthcare capacity over time in relation to epidemic dynamics, and various other factors) and (2) also it is unclear what is the relation between BCG vaccination at different ages and at longer times before the start of the SARS-CoV-2 epidemic and BCG vaccination at different ages during the SARS-CoV-2 epidemic at shorter times before the risk of possible infection; at least some of these considerations are also made or pointed out in the data analyses cited and in the article. The article [545] also

includes various related considerations such as efficacy in related animal and human studies and the safety of the vaccine, both generally and specifically with respect to SARS-CoV-2. Additionally, we review here one of the most important considerations: severe SARS-CoV-2 has been characterized so far to possibly exhibit dysregulated immune responses and whether or when some immune responses are protective or pathogenic is still under research (e.g., [88,89,92,545]); also, trained immunity itself may sometimes be related to either balanced, or too much or too little, or useful or harmful immunological responses. The article [545] proposes that trained immunity might lead to an earlier stronger response which could reduce viremia and avoid (possibly with the additional support of another therapeutic administered later) the later detrimental immunopathology seen with severe cases; while this is a possibility, additional research is required to assess its validity.

In the longer term, as more information becomes available about the structures of SARS-CoV-2 components, small molecule inhibitors of those components may become candidates for drug discovery. For example, crystal structures of the SARS-CoV-2 main protease have recently been resolved [561,562]. Efforts have already been in place to perform screens for small molecule inhibitors of the main protease, yielding potential hits [561]. Much work remains to be done to determine further crystal structures of other viral components, understand the relative utility of targeting different viral components, perform additional small molecule inhibitor screens, and determine the safety and efficacy of the potential inhibitors. While still nascent, work in this area is promising.

7 Discussion

As the COVID-19 pandemic continues to develop, the scientific community has responded by rapidly collecting and disseminating information about the SARS-CoV-2 virus and its ability to infect humans and other animals. This fundamental information has allowed for innovations in the areas of diagnostics and therapeutics that continue to be proposed and developed upon. In this review, we seek to explain the scientific rationale underlying these technologies and to critically evaluate the literature available about them.

7.1 Current State of Diagnostics

7.2 Current State of Therapeutics

7.3 Concerns about Equity in Healthcare

Scientific and medical research broadly is shaped by a number of biases. Some concerns include how clinical trials recruit and operate.

8 Methods

In an effort to keep pace as new information about COVID-19 and SARS-CoV-2 becomes available, this project is an open, collaborative effort that invited contributions the scientific community broadly, similar to previous efforts to develop collaborative reviews [563,564]. Contributors were recruited by word of mouth and on Twitter. Several efforts to work with existing efforts to train early-career scientists were also integrated: Appendix A contains summaries written by the students, post-docs, and faculty of the Immunology Institute at the Mount Sinai School of Medicine [565] and two of the authors were recruited through the American Physician Scientist Association's Virtual Summer Research Program [566]. The project was managed through GitHub [567] using Manubot [12] to continuously generate a version of the manuscript online [568]. Contributors developed text that was

proposed through GitHub's pull request system and then reviewed and approved by at least one other author. While this document reflects the current version of record, the online version will continue to be developed as information about the pandemic emerges. Below, we will describe the processes used to synthesize the literature.

8.1 Technical Infrastructure

8.1.1 Collaborative Writing and Manuscript Generation

Manubot [12] is a collaborative writing framework developed to adapt open-source software development techniques and version control for manuscript development. Here, Manubot was used to generate a manuscript from text maintained using GitHub, a popular, online version control interface. The GitHub implementation allowed users to contribute either using git on the command line or using the GitHub user interface, and we developed documentation for users with less experience with this platform. Manubot also provides a functionality to create a bibliography using digital object identifiers (DOIs), website URLs, or other identifiers such as PubMed identifiers and arXiv IDs [12]. Due to the needs of this project, project contributors also submitted pull requests to add support for clinical trial identifiers. Finally, the use of Manubot and GitHub allowed for scripted updates to be run each time the manuscript was generated. These updates were used to check that the manuscript was complete and to dynamically update information in the manuscript.

8.1.2 Data Analysis and Visualization

The combination of Manubot and GitHub Actions made it possible to integrate up-to-date analyses and visualizations of online data sources into the manuscript. Data about worldwide cases and deaths from the COVID-19 Data Repository by the Center for Systems Science and Engineering at Johns Hopkins University [5] read using a Python script to generate Figure 1. Similarly, Figure 3 was generated based on data from the University of Oxford Evidence-Based Medicine (EBM) Data Lab's COVID-19 TrialsTracker [253]. In both cases, frequency data was plotted using Matplotlib in Python. Figure ?? was generated using the countries associated with the trials listed in the EBM's COVID-19 TrialsTracker, converting the country names to 3-letter ISO codes using pycountry or manual adjustment when necessary, and visualizing the geographic distribution of trial recruitment using geopandas. Current version information for packages and software is available in <https://github.com/greenelab/covid19-review/blob/external-resources/environment.yml>.

8.2 Article Selection and Evaluation

Relevant articles were identified and submitted as issues on [GitHub](#) for review. Articles were classified as *diagnostic*, *therapeutic*, or *other*, and a template was developed to guide the review of papers and preprints in each category. Following a framework often used for assessing medical literature, the review consisted of examining methods used in each relevant article, assignment (whether the study was observational or randomized), assessment, results, interpretation, and how well the study extrapolates [569]. For examples of each template, please see Appendices B-D.

8.2.1 Diagnostic Papers

8.2.1.1 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, countries / regions considered in case of human subjects, 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.

8.2.1.2 Assignment

Reviewers described how new and reference tests were assigned, including additional relevant details about the study design. For example, reviewers were asked whether the diagnostic test resulted in rigorous assignments of case status or was biased towards sicker or healthier individuals.

8.2.1.3 Assessment

Reviewers described how the test was performed. For example, for both standard and reference tests, reviewers described technical details of assays used, when measurements were taken and by whom. Subsequently, they described how individuals were classified as positive or negative cases and whether results were precise and reproducible with repeated tests. Reviewers described whether there were any missing data, whether some participants underwent only one test, or whether there were individuals with inconclusive results.

8.2.1.4 Results

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

8.2.1.5 Interpretation

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

8.2.1.6 Extrapolation

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

8.2.2 Therapeutic Papers

8.2.2.1 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, countries / regions considered in case of human subjects, demographics of participants, the setting, and any remaining inclusion / exclusion criteria considered.

8.2.2.2 Assignment

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

8.2.2.3 Assessment

8.2.2.3.1 Outcome Assessment

Reviewers described the outcome that was assessed and evaluated whether it was appropriate given the underlying study question. They described whether there were any missing data such as whether

there were individuals lost to follow up. They then describe whether there were any potential sources of bias such as lack of blinding in a randomized controlled trial.

8.2.2.3.2 Statistical Methods Assessment

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

8.2.2.4 Results

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

8.2.2.5 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.

8.2.2.6 Extrapolation

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

9 Additional Items

9.1 Competing Interests

Author	Competing Interests	Last Reviewed
Halie M. Rando	None	2020-03-22
Casey S. Greene	None	2020-08-13
Michael P. Robson	None	2020-03-23
Simina M. Boca	None	2020-08-12
Nils Wellhausen	None	2020-03-22
Ronan Lordan	None	2020-08-13
Christian Brueffer	Employee and shareholder of SAGA Diagnostics AB.	2020-04-14
Sadipan Ray	None	2020-03-25
Lucy D'Agostino McGowan	None	2020-03-26
Anthony Gitter	Filed a provisional patent application with the Wisconsin Alumni Research Foundation related to classifying activated T cells	2020-08-12
Ronnie M. Russell	None	2020-04-07
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
Bharath Ramsundar	None	2020-04-06
Adam L. MacLean	None	2020-04-06
Alexandra J. Lee	None	2020-04-07
Immunology Institute of the Icahn School of Medicine	None	2020-04-07
Fengling Hu	None	2020-04-08
Nafisa M. Jadavji	None	2020-04-09
Elizabeth Sell	None	2020-04-10
Jinhui Wang	None	2020-04-13
Diane N. Rafizadeh	None	2020-04-14
Ashwin N. Skelly	None	2020-04-16
Marouen Ben Guebila	None	2020-04-17
Likhitha Kolla	None	2020-04-23
David Manheim	None	2020-04-28
Soumita Ghosh	None	2020-04-28

Author	Competing Interests	Last Reviewed
Matthias Fax	None	2020-04-30
James Brian Byrd	Funded by FastGrants to conduct a COVID-19-related clinical trial	2020-04-23
YoSon Park	None	2020-04-30
Vikas Bansal	None	2020-05-26
Stephen Capone	None	2020-08-12
John J. Dziak	None	2020-08-12
YuCheng Sun	None	2020-07-09
Yanjun Qi	None	2020-07-09
Lamonica Shinholster	None	2020-07-22
Sergey Knyazev	None	2020-08-03
Dimitri Perrin	None	2020-08-11
Serghei Mangul	None	2020-08-07
Shikta Das	None	2020-08-13

9.2 Author Contributions

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

Author	Contributions
Alexandra J. Lee	Writing - Original Draft
Immunology Institute of the Icahn School of Medicine	Data Curation
Fengling Hu	Writing - Original Draft, Writing - Review & Editing
Nafisa M. Jadavji	Writing - Original Draft, Writing - Review & Editing
Elizabeth Sell	Writing - Original Draft, Writing - Review & Editing
Jinhui Wang	Writing - Revising & Editing
Diane N. Rafizadeh	Writing - Original Draft, Writing - Review & Editing
Ashwin N. Skelly	Writing - Original Draft, Writing - Review & Editing
Marouen Ben Guebila	Writing - Original Draft
Likhitha Kolla	Writing - Original Draft
David Manheim	Writing - Original Draft, Investigation
Soumita Ghosh	Writing - Original Draft
Matthias Fax	Writing - Review & Editing
James Brian Byrd	Writing - Original Draft, Writing - Review & Editing
YoSon Park	Writing - Original Draft, Writing - Review & Editing, Investigation
Vikas Bansal	Writing - Original Draft, Investigation
Stephen Capone	Writing - Review & Editing, Writing - Original Draft
John J. Dziak	Writing - Original Draft
YuCheng Sun	Visualization
Yanjun Qi	Visualization
Lamonica Shinholster	Writing - Original Draft
Sergey Knyazev	Writing - Original Draft
Dimitri Perrin	Writing - Original Draft, Writing - Review & Editing
Serghei Mangul	Writing - Review & Editing
Shikta Das	Writing - Review & Editing

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Bruna GG Pinto, Antonio ER Oliveira, Youvika Singh, Leandro Jimenez, Andre NA Goncalves, Rodrigo LT Ogava, Rachel Creighton, Jean PS Peron, Helder I Nakaya

medRxiv (2020-03-27) <https://doi.org/ggg65k>

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667. Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial

Huijie Bian, Zhao-Hui Zheng, Ding Wei, Zheng Zhang, Wen-Zhen Kang, Chun-Qiu Hao, Ke Dong, Wen Kang, Jie-Lai Xia, Jin-Lin Miao, ... Ping Zhu

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668. CD147 facilitates HIV-1 infection by interacting with virus-associated cyclophilin A

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669. CD147/EMMPRIN Acts as a Functional Entry Receptor for Measles Virus on Epithelial Cells

Akira Watanabe, Misako Yoneda, Fusako Ikeda, Yuri Terao-Muto, Hiroki Sato, Chieko Kai

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670. Basigin is a receptor essential for erythrocyte invasion by Plasmodium falciparum

Cécile Crosnier, Leyla Y. Bustamante, S. Josefin Bartholdson, Amy K. Bei, Michel Theron, Makoto Uchikawa, Souleymane Mboup, Omar Ndir, Dominic P. Kwiatkowski, Manoj T. Duraisingh, ... Gavin J. Wright

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671. Function of HAB18G/CD147 in Invasion of Host Cells by Severe Acute Respiratory Syndrome Coronavirus

Zhinan Chen, Li Mi, Jing Xu, Jiyun Yu, Xianhui Wang, Jianli Jiang, Jinliang Xing, Peng Shang, Airong Qian, Yu Li, ... Ping Zhu

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672. CD147 mediates intrahepatic leukocyte aggregation and determines the extent of liver injury

Christine Yee, Nathan M. Main, Alexandra Terry, Igor Stevanovski, Annette Maczurek, Alison J. Morgan, Sarah Calabro, Alison J. Potter, Tina L. Iemma, David G. Bowen, ... Nicholas A. Shackel
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673. Characterisation of the transcriptome and proteome of SARS-CoV-2 using direct RNA sequencing and tandem mass spectrometry reveals evidence for a cell passage induced in-frame deletion in the spike glycoprotein that removes the furin-like cleavage site

Andrew D. Davidson, Maia Kavanagh Williamson, Sebastian Lewis, Deborah Shoemark, Miles W. Carroll, Kate Heesom, Maria Zambon, Joanna Ellis, Phillip A. Lewis, Julian A. Hiscox, David A. Matthews
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676. First Clinical Study Using HCV Protease Inhibitor Danoprevir to Treat Naive and Experienced COVID-19 Patients

Hongyi Chen, Zhicheng Zhang, Li Wang, Zhihua Huang, Fanghua Gong, Xiaodong Li, Yahong Chen, Jinzi J. WU
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677. Preclinical Characteristics of the Hepatitis C Virus NS3/4A Protease Inhibitor ITMN-191 (R7227)

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678. Efficacy and Safety of All-oral, 12-week Ravidasvir Plus Ritonavir-boosted Danoprevir and Ribavirin in Treatment-naïve Noncirrhotic HCV Genotype 1 Patients: Results from a Phase 2/3 Clinical Trial in China

Xiaoyuan Xu, Bo Feng, Yujuan Guan, Sujun Zheng, Jifang Sheng, Xingxiang Yang, Yuanji Ma, Yan Huang, Yi Kang, Xiaofeng Wen, ... Lai Wei
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679. Potentially highly potent drugs for 2019-nCoV

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680. **Serology characteristics of SARS-CoV-2 infection since the exposure and post symptoms onset**
Bin Lou, Tigndong Li, Shufa Zheng, Yingying Su, Zhiyong Li, Wei Liu, Fei Yu, Shengxiang Ge, Qianda Zou, Quan Yuan, ... Yu Chen
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681. **SARS-CoV-2 launches a unique transcriptional signature from in vitro, ex vivo, and in vivo systems**
Daniel Blanco-Melo, Benjamin E. Nilsson-Payant, Wen-Chun Liu, Rasmus Møller, Maryline Panis, David Sachs, Randy A. Albrecht, Benjamin R. tenOever
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682. **A New Predictor of Disease Severity in Patients with COVID-19 in Wuhan, China**
Ying Zhou, Zhen Yang, Yanan Guo, Shuang Geng, Shan Gao, Shenglan Ye, Yi Hu, Yafei Wang
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684. **Viral Kinetics and Antibody Responses in Patients with COVID-19**
Wenting Tan, Yanqiu Lu, Juan Zhang, Jing Wang, Yunjie Dan, Zhaoxia Tan, Xiaoqing He, Chunfang Qian, Qiangzhong Sun, Qingli Hu, ... Guohong Deng
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685. **Global profiling of SARS-CoV-2 specific IgG/ IgM responses of convalescents using a proteome microarray**
He-wei Jiang, Yang Li, Hai-nan Zhang, Wei Wang, Dong Men, Xiao Yang, Huan Qi, Jie Zhou, Sheng-ce Tao
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686. **COVID-19 infection induces readily detectable morphological and inflammation-related phenotypic changes in peripheral blood monocytes, the severity of which correlate with patient outcome**
Dan Zhang, Rui Guo, Lei Lei, Hongjuan Liu, Yawen Wang, Yili Wang, Tongxin Dai, Tianxiao Zhang, Yanjun Lai, Jingya Wang, ... Jinsong Hu
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DOI: [10.1101/2020.03.24.20042655](https://doi.org/10.1101/2020.03.24.20042655)
687. **Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study**
Aaron Miller, Mac Josh Reandelar, Kimberly Fasciglione, Violeta Roumenova, Yan Li, Gonzalo H Otazu
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Murdoch Children's Research Institute
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690. **Non-neural expression of SARS-CoV-2 entry genes in the olfactory epithelium suggests mechanisms underlying anosmia in COVID-19 patients**
David H. Brann, Tatsuya Tsukahara, Caleb Weinreb, Darren W. Logan, Sandeep Robert Datta
bioRxiv (2020-03-28) <https://doi.org/ggqr4m>
DOI: [10.1101/2020.03.25.009084](https://doi.org/10.1101/2020.03.25.009084)
691. **Cigarette smoke triggers the expansion of a subpopulation of respiratory epithelial cells that express the SARS-CoV-2 receptor ACE2**
Joan C Smith, Jason Meyer Sheltzer
bioRxiv (2020-03-31) <https://doi.org/ggq65x>
DOI: [10.1101/2020.03.28.013672](https://doi.org/10.1101/2020.03.28.013672)
692. **The comparative superiority of IgM-IgG antibody test to real-time reverse transcriptase PCR detection for SARS-CoV-2 infection diagnosis**
Rui Liu, Xinghui Liu, Huan Han, Muhammad Adnan Shereen, Zhili Niu, Dong Li, Fang Liu, Kailang Wu, Zhen Luo, Chengliang Zhu
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11 Appendix 1

This appendix contains reviews produced by the Immunology Institute of the Icahn School of Medicine

11.1 Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody

Tian et al. *Emerg Microbes Infect* 2020 [[570](#)]

11.1.1 Keywords

- Monoclonal antibody
- Cross-reactivity
- receptor binding domain

11.1.2 Summary

Considering the relatively high identity of the receptor binding domain (RBD) of the spike proteins from 2019-nCoV and SARS-CoV (73%), this study aims to assess the cross-reactivity of several anti-SARS-CoV monoclonal antibodies with 2019-nCoV. The results showed that the SARS-CoV-specific antibody CR3022 can potentially bind 2019-nCoV RBD.

11.1.3 Main Findings

The structure of the 2019-nCoV spike RBD and its conformation in complex with the receptor angiotensin-converting enzyme (ACE2) was modeled *in silico* and compared with the SARS-CoV RBD structure. The models predicted very similar RBD-ACE2 interactions for both viruses. The binding capacity of representative SARS-CoV-RBD specific monoclonal antibodies (m396, CR3014, and CR3022) to recombinant 2019-nCoV RBD was then investigated by ELISA and their binding kinetics studied using biolayer interferometry. The analysis showed that only CR3022 was able to bind 2019-nCoV RBD with high affinity (KD of 6.3 nM), however it did not interfere with ACE2 binding. Antibodies m396 and CR3014, which target the ACE2 binding site of SARS-CoV failed to bind 2019-nCoV spike protein.

11.1.4 Limitations

The 2019-nCoV RBD largely differ from the SARS-CoV at the C-terminus residues, which drastically impact the cross-reactivity of antibodies described for other B beta-coronaviruses, including SARS-CoV. This study claims that CR3022 antibody could be a potential candidate for therapy. However, none of the antibodies assayed in this work showed cross-reactivity with the ACE2 binding site of 2019-nCoV, essential for the replication of this virus. Furthermore, neutralization assays with 2019-nCoV virus or pseudovirus were not performed. Although the use of neutralizing antibodies is an interesting approach, these results suggest that it is critical the development of novel monoclonal antibodies able to specifically bind 2019-nCoV spike protein.

11.1.5 Credit

Review by D.L.O as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.2 Integrative Bioinformatics Analysis Provides Insight into the Molecular Mechanisms of 2019-nCoV

He et al. *medRxiv* [[571](#)]

11.2.1 Keywords

- ACE2
- lungs
- smoking
- COPD
- asthma
- SARS-Cov
- IL-1
- IL-10
- IL-6
- IL-8

11.2.2 Main Findings

The authors used bioinformatics tools to identify features of ACE2 expression in the lungs of different patient groups: healthy, smokers, patients with chronic airway disease (i.e., COPD) or asthma. They used gene expression data publicly available from GEO that included lung tissues, bronchoalveolar lavage, bronchial epithelial cells, small airway epithelial cells, or SARS-Cov infected cells.

The authors describe no significant differences in ACE2 expression in lung tissues of Healthy, COPD, and Asthma groups ($p=0.85$); or in BAL of Healthy and COPD ($p=0.48$); or in epithelial brushings of Healthy and Mild/Moderate/Severe Asthma ($p=0.99$). ACE2 was higher in the small airway epithelium of long-term smokers vs non-smokers ($p<0.001$). Consistently, there was a trend of higher ACE2 expression in the bronchial airway epithelial cells 24h post-acute smoking exposure ($p=0.073$). Increasing ACE2 expression at 24h and 48h compared to 12h post SARS-Cov infection ($p=0.026$; $n=3$ at each time point) was also detected.

15 lung samples' data from healthy participants were separated into high and low ACE2 expression groups. "High" ACE2 expression was associated with the following GO pathways: innate and adaptive immune responses, B cell mediated immunity, cytokine secretion, and IL-1, IL-10, IL-6, IL-8 cytokines. The authors speculate that a high basal ACE2 expression will increase susceptibility to SARS-CoV infection.

In 3 samples SARS-Cov infection was associated with IL-1, IL-10 and IL-6 cytokine production (GO pathways) at 24h. And later, at 48h, with T-cell activation and T-cell cytokine production. It is unclear whether those changes were statistically significant.

The authors describe a time course quantification of immune infiltrates in epithelial cells infected with SARS-Cov infection. They state that in healthy donors ACE2 expression did not correlate with the immune cell infiltration. However, in SARS-Cov samples, at 48h they found that ACE2 correlated with neutrophils, NK-, Th17-, Th2-, Th1- cells, and DCs. Again, while authors claim significance, the corresponding correlation coefficients and p-values are not presented in the text or figures. In addition, the source of the data for this analysis is not clear.

Using network analysis, proteins SRC, FN1, MAPK3, LYN, MBP, NLRC4, NLRP1 and PRKCD were found to be central (Hub proteins) in the regulating network of cytokine secretion after coronavirus

infection. Authors conclude this indicates that these molecules were critically important in ACE2-induced inflammatory response. Additionally, authors speculate that the increased expression of ACE2 affected RPS3 and SRC, which were the two hub genes involved in viral replication and inflammatory response.

11.2.3 Limitations

The methods section is very limited and does not describe any of the statistical analyses; and description of the construction of the regulatory protein networks is also limited. For the findings in Figures 2 authors claim significance, which is not supported by p-values or coefficients. For the sample selection, would be useful if sample sizes and some of the patients' demographics (e.g. age) were described.

For the analysis of high vs low ACE2 expression in healthy subjects, it is not clear what was the cut off for 'high' expression and how it was determined. Additionally, further laboratory studies are warranted to confirm that high ACE2 gene expression would have high correlation with the amount of ACE2 protein on cell surface. For the GO pathway analysis significance was set at $p < 0.05$, but not adjusted for multiple comparisons.

There were no samples with SARS-CoV-2 infection. While SARS-Cov and SARS-CoV-2 both use ACE2 to enter the host cells, the analysis only included data on SARS-Cov and any conclusions about SARS-CoV2 are limited.

Upon checking GSE accession numbers of the datasets references, two might not be cited correctly: GSE37758 ("A *spargillus niger*: Control (fructose) vs. steam-exploded sugarcane induction (SEB)"" was used in this paper as "lung tissue" data) and GSE14700 ("Steroid Pretreatment of Organ Donors to Prevent Postischemic Renal Allograft Failure: A Randomized, Controlled Trial" – was used as SARS-Cov infection data).

11.2.4 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.3 Diarrhea may be underestimated: a missing link in 2019 novel coronavirus

Liang et al. *medRxiv* [[572](#)]

11.3.1 Keywords

- SARS-CoV-2
- diarrhea
- ACE2
- scRNA-seq

11.3.2 Main Findings

This study examined the incidence of diarrhea in patients infected with SARS-CoV-2 across three recently published cohorts and found that there are statistically significant differences by Fisher's exact test. They report that this could be due to subjective diagnosis criterion for diarrhea or from patients first seeking medical care from gastroenterologist. In order to minimize nosocomial

infections arising from unsuspected patients with diarrhea and gain comprehensive understanding of transmission routes for this viral pathogen, they compared the transcriptional levels of ACE2 of various human tissues from NCBI public database as well as in small intestine tissue from CD57BL/6 mice using single cell sequencing. They show that ACE2 expression is not only increased in the human small intestine, but demonstrate a particular increase in mice enterocytes positioned on the surface of the intestinal lining exposed to viral pathogens. Given that ACE2 is the viral receptor for SARS-CoV-2 and also reported to regulate diarrhea, their data suggests the small intestine as a potential transmission route and diarrhea as a potentially underestimated symptom in COVID19 patients that must be carefully monitored. Interestingly, however, they show that ACE2 expression level is not elevated in human lung tissue.

11.3.3 Limitations

Although this study demonstrates a statistical difference in the incidence of diarrhea across three separate COVID19 patient cohorts, their conclusions are limited by a small sample size. Specifically, the p-value computed by Fisher's exact test is based on a single patient cohort of only six cases of which 33% are reported to have diarrhea, while the remaining two larger cohorts with 41 and 99 cases report 3% and 2% diarrhea incidence, respectively. Despite showing significance, they would need to acquire larger sample sizes and cohorts to minimize random variability and draw meaningful conclusions. Furthermore, they do not address why ACE2 expression level is not elevated in human lung tissue despite it being a major established route of transmission for SARS-CoV-2. It could be helpful to validate this result by looking at ACE2 expression in mouse lung tissue. Finally, although this study is descriptive and shows elevated ACE2 expression in small intestinal epithelial cells, it does not establish a mechanistic link to SARS-CoV-2 infection of the host. Overall, their claim that infected patients exhibiting diarrhea pose an increased risk to hospital staff needs to be further substantiated.

11.3.4 Significance

This study provides a possible transmission route and a potentially underappreciated clinical symptom for SARS-CoV-2 for better clinical management and control of COVID19.

11.3.5 Credit

Summary generated as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.4 Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection

Chai et al. *bioRxiv* [[573](#)]

11.4.1 Keywords

- ACE2
- Cholangiocytes
- COVID-associated Liver Damage

11.4.2 Summary

Using both publicly available scRNA-seq dataset of liver samples from colorectal patients and scRNA-sequencing of four liver samples from healthy volunteers, the authors show that ACE2 is significantly enriched in the majority of cholangiocytes (59.7 %) but not in hepatocytes (2.6%).

11.4.3 Main Findings

Using bioinformatics approaches of RNASeq analysis, this study reveals that ACE2 dominates in cholangiocytes and is present at very low levels in hepatocytes.

11.4.4 Limitations

The study does not provide mechanistic insights into how SARS-CoV-2 can infect and replicate in cholangiocytes and the types of intrinsic anti-viral responses induced by cholangiocytes when infected. In addition, because the study relies on the assumption that SARS-CoV-2 infects cells only through ACE2, it cannot discount the possibility that the virus can infect hepatocytes through mechanisms other than ACE2-mediated entry. Furthermore, because the scRNA-seq analysis were performed on healthy liver samples, one cannot draw any definitive conclusions about gene expression states (including ACE2 expression in liver cell types) in system-wide inflammatory contexts.

11.4.5 Significance

This article with other studies on liver damage in COVID patients suggests that liver damage observed in COVID patients is more due to inflammatory cytokines than direct infection of the liver. Even if cholangiocytes are infectable by SARS-CoV-2 (which was demonstrated by human liver ductal organoid study ([574])), published clinical data show no significant increase in bile duct injury related indexes (i.e. alkaline phosphatase, gamma-glutamyl transpeptidase and total bilirubin). In sum, it underscores the importance of future studies characterizing cellular responses of extra-pulmonary organs in the context of COVID or at least in viral lung infections..

11.4.6 Credit

Summary generated by Chang Moon as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.5 ACE2 expression by colonic epithelial cells is associated with viral infection, immunity and energy metabolism

Wang et al. *medRxiv*. [575]

11.5.1 Keywords

- single cell RNA seq
- ACE2 expression
- human colonic biopsy

11.5.2 Main Findings

Colonic enterocytes primarily express ACE2. Cellular pathways associated with ACE2 expression include innate immune signaling, HLA up regulation, energy metabolism and apoptotic signaling.

11.5.3 Limitations

This is a study of colonic biopsies taken from 17 children with and without IBD and analyzed using scRNAseq to look at ACE2 expression and identify gene families correlated with ACE2 expression. The authors find ACE2 expression to be primarily in colonocytes. It is not clear why both healthy and IBD patients were combined for the analysis. Biopsies were all of children so extrapolation to adults is

limited. The majority of genes found to be negatively correlated with ACE2 expression include immunoglobulin genes (IGs). IG expression will almost certainly be low in colonocytes irrespective of ACE2 expression.

11.5.4 Significance

This study performs a retrospective analysis of ACE2 expression using an RNAseq dataset from intestinal biopsies of children with and without IBD. The implications for the CoV-19 epidemic are modest, but do provide support that ACE2 expression is specific to colonocytes in the intestines. The ontological pathway analysis provides some limited insights into gene expression associated with ACE2.

11.5.5 Credit

Summary generated as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.6 The Pathogenicity of 2019 Novel Coronavirus in hACE2 Transgenic Mice

Bao et al. *bioRxiv* [[576](#)]

11.6.1 Keywords

- Covid-19 mouse model
- hACE2 mice
- 2019-nCoV model
- ACE2
- 2019-nCoV

11.6.2 Main Findings

Using a transgenic human Angiotensin-converting enzyme 2 (hACE2) mouse that has previously been shown susceptible to infection by SARS-CoV, Bao et al. create a model of pandemic 2019-nCoV strain coronavirus. The model includes interstitial hyperplasia in lung tissue, moderate inflammation in bronchioles and blood vessels, and histology consistent with viral pneumonia at 3 days post infection. Wildtype did not experience these symptoms. In addition, viral antigen and hACE2 receptor were found to co-localize the lung by immunofluorescence 3-10 days post infection only in the hACE2 infected mice.

11.6.3 Limitations

The characterization of the infection remains incomplete, as well as lacking characterization of the immune response other than the presence of a single antiviral antibody. Though they claim to fulfill Koch's postulates, they only isolate the virus and re-infect Vero cells, rather than naive mice.

11.6.4 Significance

This paper establishes a murine model for 2019-nCoV infection with symptoms consistent with viral pneumonia. Though not fully characterized, this model allows in vivo analysis of viral entry and pathology that is important for the development of vaccines and antiviral therapeutics.

11.6.5 Credit

11.7 Caution on Kidney Dysfunctions of 2019-nCoV Patients

Li et al. *medRxiv*. [[577](#)]

11.7.1 Keywords

CoVID-19, 2019-nCoV, SARS-CoV-2, kidney, clinical, creatinine, proteinuria, albuminuria, CT

11.7.2 Main Findings

- Retrospective study of 59 patients assayed key function indicators of the kidney—including urine protein, blood urea nitrogen (BUN), plasma creatinine (Cre), and renal CT scan data.
- Found that 34% of patients developed massive albuminuria on the first day of admission, and 63% developed proteinuria during their stay in hospital; and 19% of patients had high plasma creatinine, especially the terminal cases.
- CT analyses of 27 patients showed all patients to have abnormal kidney damage; indicate that inflammation and edema of the renal parenchyma very common.

11.7.3 Limitations

- No analysis of immunity-dependent damage and cytokines in blood/plasma/urine. Will be worth correlating disease progression with cytokine production, immune activity and kidney function.
- Extrapolating to earlier SARS-CoV studies provides the only rationale for viral-damage in kidney and resultant pathologic immune response (*understandable for this clinical study*).

11.7.4 Significance

- Multiple lines of evidence along this study's finding point to the idea that renal impairment/injury is a key risk factor in 2019-nCoV patients similar to what has been reported for SARS-CoV [[578](#)]; this may be one of the major causes of virally-induced damage and contribute to multiorgan failure.
- ACE2 expression in kidney proximal tubule epithelia and bladder epithelia [[579](#)] support these clinical findings.
- Study argues for closely monitoring kidney function, and applying potential interventions including continuous renal replacement therapies (CRRT) for protecting kidney functions as early as possible, particularly for those with rising plasma creatinine.

11.7.5 Credit

Review by Samarth Hegde as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.8 Profiling the immune vulnerability landscape of the 2019 Novel Coronavirus

11.8.1 Keywords

- epitope prediction
- vaccine development.

11.8.2 Main Findings

This study harnesses bioinformatic profiling to predict the potential of COV2 viral proteins to be presented on MHC I and II and to form linear B-cell epitopes. These estimates suggest a T-cell antigenic profile distinct from SARS-CoV or MERS-CoV, identify focused regions of the virus with a high density of predicted epitopes, and provide preliminary evidence for adaptive immune pressure in the genetic evolution of the virus.

11.8.3 Limitations

While the study performs a comprehensive analysis of potential epitopes within the virus genome, the analysis relies solely on bioinformatic prediction to examine MHC binding affinity and B-cell epitope potential and does not capture the immunogenicity or recognition of these epitopes. Future experimental validation in data from patients infected with SARS-CoV-2 will be important to validate and refine these findings. Thus some of the potential conclusions stated, including viral evolution toward lower immunogenicity or a dominant role for CD4+ T-cells rather than CD8+ T-cells in viral clearance, require further validation.

11.8.4 Significance

These findings may help direct peptide vaccine design toward relevant epitopes and provide intriguing evidence of viral evolution in response to immune pressure.

11.8.5 Credit

Summary generated as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.9 Single-cell Analysis of ACE2 Expression in Human Kidneys and Bladders Reveals a Potential Route of 2019-nCoV Infection

11.9.1 Keywords

- CoVID-19
- 2019-nCoV
- SARS-CoV-2
- ACE2
- scRNAseq
- kidney
- bladder
- public dataset

11.9.2 Main Findings

- To investigate the possible cause of kidney damage in 2019-nCoV patients, authors used published kidney and bladder cell atlas data (GSE131685, GSE108097; 3 healthy donors each) as well as an unpublished kidney single-cell RNA-Seq data (in-house from 2 transplant donors) to evaluate ACE2 gene expressions in all cell types of healthy kidneys and bladders.
- They find enriched expression of ACE2 transcript in all subtypes of proximal tubule cells of kidney, with 5%-15% of both straight and convoluted proximal tubule cells expressing ACE2.
- They also find detectable levels of ACE2 in bladder epithelial cells, noting expression from around 1.5% of cells in the outer layer umbrella cells of the bladder epithelium and decreasing in the basal cells.
- Importantly endothelial or immune cells in kidney/bladder do not express ACE2.

11.9.3 Limitations

- This study primarily characterizes ACE2 expression (amongst other genes) from a small healthy-donor dataset, and will benefit from supporting data in (expired) patient samples to show functional viral damage. ACE2 transcript does not necessarily translate to viral permissiveness in kidney/bladder epithelia or cytokine release.
- This study focuses on only healthy tissue; it will be useful to analyze kidney/bladder epithelial ACE2 expression under inflammatory conditions or in patients with underlying kidney conditions.
- Given what is known about protease TMPRSS2 expression during SARS-CoV-2 infection, ACE2+TMPRSS2+ double-positive cell identification would be useful in these datasets.

11.9.4 Significance

- ACE2 protein is spatially restricted to brush border of proximal tubules and in bladder umbrella cells [[581](#)], such cells in direct contact with viral particles are likely to be highly sensitive to viral-induced damage.
- SARS-CoV and MERS-CoV have been shown to be detected in urine of patients and associate with higher mortality [[578](#), [582](#)], thus worth understanding kidney damage and resultant immune response in SARS-CoV-2 as well.
- This study argues for a potential mode of viral infectivity and resultant inflammatory responses in these tissue in addition to reported infectivity in the lung and digestive system, which is supported by clinical data showing acute and early kidney complications in 2019-nCoV patients [[577](#)].
- Clinically, thus very important to track urinary CoVID-19 shedding as well as study acute kidney injury-related co-morbidities.

11.9.5 Credit

Review by Samarth Hegde as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.10 Neutrophil-to-Lymphocyte Ratio Predicts Severe Illness Patients with 2019 Novel Coronavirus in the Early Stage

11.10.1 Keywords

- severe disease
- pneumonia
- lymphocytes
- neutrophils

11.10.2 Main Findings

This study aimed to find prognostic biomarkers of COVID-19 pneumonia severity. Sixty-one (61) patients with COVID-19 treated in January at a hospital in Beijing, China were included. On average, patients were seen within 5 days from illness onset. Samples were collected on admission; and then patients were monitored for the development of severe illness with a median follow-up of 10 days].

Patients were grouped as “mild” (N=44) or “moderate/severe” (N=17) according to symptoms on admission and compared for different clinical/laboratory features. “Moderate/severe” patients were significantly older (median of 56 years old, compared to 41 years old). Whereas comorbidities rates were largely similar between the groups, except for hypertension, which was more frequent in the severe group ($p=0.056$). ‘Severe’ patients had higher counts of neutrophils, and serum glucose levels; but lower lymphocyte counts, sodium and serum chlorine levels. The ratio of neutrophils to lymphocytes (NLR) was also higher for the ‘severe’ group. ‘Severe’ patients had a higher rate of bacterial infections (and antibiotic treatment) and received more intensive respiratory support and treatment.

26 clinical/laboratory variables were used to select NLR and age as the best predictors of the severe disease. Predictive cutoffs for a severe illness as $NLR \geq 3.13$ or $age \geq 50$ years.

11.10.3 Limitations

Identification of early biomarkers is important for making clinical decisions, but large sample size and validation cohorts are necessary to confirm findings. It is worth noting that patients classified as “mild” showed pneumonia by imaging and fever, and in accordance with current classifications this would be consistent with “moderate” cases. Hence it would be more appropriate to refer to the groups as “moderate” vs “severe/critical”. Furthermore, there are several limitations that could impact the interpretation of the results: e.g. classification of patients was based on symptoms presented on admission and not based on disease progression, small sample size, especially the number of ‘severe’ cases (with no deaths among these patients). Given the small sample size, the proposed NLR and age cut offs might not hold for a slightly different set of patients. For example, in a study of >400 patients, ‘non-severe’ and ‘severe’ NLR were 3.2 and 5.5, respectively [584].

11.10.4 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.11 Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP)

11.11.1 Keywords

- Cytokines
- lymphocyte subsets
- CD8 + T
- B cells
- NK cells,
- PBMCs
- IL-6
- IL-10

11.11.2 Main Findings

The authors analyzed lymphocyte subsets and cytokines of 102 patients with mild disease and 21 with severe disease. CD8+T cells and CD4+T cells were significantly reduced in both cohort, particularly in severe patients. The cytokines IL6 and IL10 were significantly elevated in severe patients as compared to mild. No significant differences were observed in frequency of B cells and NK cells.

The authors argue that the measurement of T cell frequencies and cytokine levels of IL6 and IL10 can be used to predict progression of disease from Mild to severe Cov-2 infection.

11.11.3 Limitations

The study demonstrates in a limited cohort similar associations to several other reported studies. The authors didn't compare the changes in lymphocyte and cytokine with healthy individual (Covid-19 Negative) rather used an internal standard value. The recently preprint in LANCET shows The degree of lymphopenia and a pro-inflammatory cytokine storm is higher in severe COVID-19 patients than in mild cases, and is associated with the disease severity [[586](#)].

11.11.4 Significance

This translational data identifies key cytokines and lymphopenia associated with disease severity although mechanism and key cellular players are still unknown. Higher level IL-6 production in severe patient suggests potential role of Tocilizumab (anti-IL6R) biologic although clinical trial will be necessary.

11.11.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.12 Epidemiological and Clinical Characteristics of 17 Hospitalized Patients with 2019 Novel Coronavirus Infections Outside Wuhan, China

Li et al. *medRxiv* [[587](#)]

11.12.1 Keywords

- epidemiology
- clinical characteristics

11.12.2 Major Findings

These authors looked at 17 hospitalized patients with COVID-19 confirmed by RT-PCR in Dazhou, Sichuan. Patients were admitted between January 22 and February 10 and the final data were collected on February 11. Of the 17 patients, 12 remained hospitalized while 5 were discharged after meeting national standards. The authors observed no differences based on the sex of the patients but found that the discharged patients were younger in age ($p = 0.026$) and had higher lymphocyte counts ($p = 0.005$) and monocyte counts ($p = 0.019$) upon admission.

11.12.3 Limitations

This study is limited in the sample size of the study and the last data collection point was only one day after some of the patients were admitted.

11.12.4 Significance

These findings have been somewhat supported by subsequent studies that show that older age and an immunocompromised state are more likely to result in a more severe clinical course with COVID-19. However, other studies have been published that report on larger numbers of cases.

11.12.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.13 ACE2 Expression in Kidney and Testis May Cause Kidney and Testis Damage After 2019-nCoV Infection

[\[588\]](#)

11.13.1 Keywords

- CoVID-19
- 2019-nCoV
- SARS-CoV-2
- kidney
- testis
- ACE2
- scRNAseq

11.13.2 Main Findings

- Study used online datasets (scRNAseq GSE131685, scRNAseq GSE107585, Human Protein Atlas, GTEx portal, CCLE) to analyze ACE2 expression in different human organs.
- Study re-analyzed three clinical datasets ($n=6$, $n=99$, and $n=41$) to show 3~10% of 2019-nCoV patients present with abnormal renal function.
- results indicate ACE2 highly expressed in renal tubular cells, Leydig cells and seminiferous ductal cells of testis.

11.13.3 Limitations

- Very preliminary transcript/protein dataset analysis in healthy cohorts; does not necessarily translate to actual viral tropism and permissiveness.
- Clinically, would be important to determine with larger longitudinal dataset if SARS-CoV-2 infection changes sperm quality or testicular inflammation.
- Similarly, would be important to determine if simultaneous HBV or syphilis infection and orchitis impacts SARS-CoV-2 severity.
- Examination and follow-up of renal function and viral orchitis/sperm quality of CoVID-19 patients not done in this preliminary study.

11.13.4 Significance

- Kidney ACE2 result supports other concurrent sequencing studies [[579](#)] and clinical reports of abnormal renal function or even kidney damage in patients infected with 2019-nCoV [[577](#)].
- High ACE2 expression in testis suggests potential tropism of the virus to testicular tissues and indicates potential risks for male fertility. Viral orchitis reported for SARS-CoV previously [1], but no clear evidence so far of infertility in SARS, MERS or CoVID-19 patients.

11.13.5 Credit

Review by Samarth Hegde as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.14 Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus

[[589](#)]

11.14.1 Keywords

- immunopathology
- Th1
- inflammatory monocytes
- GM-CSF
- IFN- γ
- IL-6

11.14.2 Main Findings

The authors of this study sought to characterize the immune mechanism causing severe pulmonary disease and mortality in 2019-nCoV (COVID-19) patients. Peripheral blood was collected from hospitalized ICU (n=12) and non-ICU (n=21) patients with confirmed 2019-nCoV and from healthy controls (n=10) in The First Affiliated Hospital of University of Science and Technology China (Hefei, Anhui). Immune analysis was conducted by flow cytometry. 2019-nCoV patients had decreased lymphocyte, monocyte, and CD4 T cell counts compared to healthy controls. ICU patients had fewer lymphocytes than non-ICU patients. CD4 T cells of 2019-nCoV patients expressed higher levels of activation markers (OX40, CD69, CD38, CD44) and exhaustion markers (PD-1 and Tim3) than those of healthy controls. CD4 cells of ICU patients expressed significantly higher levels of OX40, PD-1, and Tim3 than those of non-ICU patients. 2019-nCoV patients had higher percentages of CD4 T cells co-

expressing GM-CSF and IL-6 compared to healthy controls, while ICU patients had a markedly higher percentage of GM-CSF+ IFN- γ + CD4 T cells than non-ICU patients. The CD4 T cells of nCoV patients and healthy controls showed no differences in TNF- α secretion.

The CD8 T cells of 2019-nCoV patients also showed higher expression of activation markers CD69, CD38, and CD44, as well as exhaustion markers PD-1 and Tim3, compared to healthy controls. CD8 T cells of ICU patients expressed higher levels of GM-CSF than those of non-ICU patients and healthy controls. No IL-6 or TNF- α was found in the CD8 T cells of any group. There were no differences in numbers of NK cells or B cells in 2019-nCoV patients and healthy controls, nor was there any GM-CSF or IL-6 secretion from these cells in either group.

Percentages of CD14+ CD16+ GM-CSF+ and CD14+ CD16+ IL-6+ inflammatory monocytes were significantly increased in nCoV patients compared to healthy controls; in particular, patients in the ICU had greater percentages of CD14+ CD16+ IL-6+ monocytes than non-ICU patients. The authors suggest that in 2019-nCoV patients, pathogenic Th1 cells produce GM-CSF, recruiting CD14+ CD16+ inflammatory monocytes that secrete high levels of IL-6. These may enter pulmonary circulation and damage lung tissue while initiating the cytokine storm that causes mortality in severe cases. This is consistent with the cytokine storm seen in similar coronaviruses, as IL-6, IFN- γ , and GM-CSF are key inflammatory mediators seen in patients with SARS-CoV-1 and MERS-CoV.

11.14.3 Limitations

Though the results of this study open questions for further investigation, this is an early study on a small cohort of patients, and as such there are a number of limitations. The study included only 12 ICU patients and 21 non-ICU patients, and ideally would be repeated with a much larger patient cohort. Though the authors make claims about differences in lymphocyte and monocyte counts between patients and healthy controls, they did not report baseline laboratory findings for the control group. Additionally, severity of disease was classified based on whether or not patients were in the ICU. It would be interesting to contextualize the authors' immunological findings with more specific metrics of disease severity or time course. Noting mortality, time from disease onset, pre-existing conditions, or severity of lung pathology in post-mortem tissue samples would paint a fuller picture of how to assess risk level and the relationship between severity of disease and immunopathology. Another limitation is the selection of cytokines and immune markers for analysis, as the selection criteria were based on the cell subsets and cytokine storm typically seen in SARS-CoV-1 and MERS-CoV patients. Unbiased cytokine screens and immune profiling may reveal novel therapeutic targets that were not included in this study.

11.14.4 Significance

This study identifies potential therapeutic targets that could prevent acute respiratory disease syndrome (ARDS) and mortality in patients most severely affected by COVID-19. The authors propose testing monoclonal antibodies against IL6-R or GM-CSF to block recruitment of inflammatory monocytes and the subsequent cytokine storm in these patients.

11.14.5 Credit

Review by Gabrielle Lubitz as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.15 Clinical Characteristics of 2019 Novel Infected Coronavirus Pneumonia : A Systemic Review and Meta-analysis

11.15.1 Keywords

- White Blood Cells
- Lymphocytes
- Neutrophils

11.15.2 Main Findings

The authors performed a meta analysis of literature on clinical, laboratory and radiologic characteristics of patients presenting with pneumonia related to SARSCoV2 infection, published up to Feb 6 2020. They found that symptoms that were mostly consistent among studies were sore throat, headache, diarrhea and rhinorrhea. Fever, cough, malaise and muscle pain were highly variable across studies. Leukopenia (mostly lymphocytopenia) and increased white blood cells were highly variable across studies. They identified three most common patterns seen on CT scan, but there was high variability across studies. Consistently across the studies examined, the authors found that about 75% of patients need supplemental oxygen therapy, about 23% mechanical ventilation and about 5% extracorporeal membrane oxygenation (ECMO). The authors calculated a staggering pooled mortality incidence of 78% for these patients.

11.15.3 Limitations

The authors mention that the total number of studies included in this meta analysis is nine, however they also mentioned that only three studies reported individual patient data. It is overall unclear how many patients in total were included in their analysis. This is mostly relevant as they reported an incredibly high mortality (78%) and mention an absolute number of deaths of 26 cases overall. It is not clear from their report how the mortality rate was calculated.

The data is based on reports from China and mostly from the Wuhan area, which somewhat limits the overall generalizability and applicability of these results.

11.15.4 Significance

This meta analysis offers some important data for clinicians to refer to when dealing with patients with COVID-19 and specifically with pneumonia. It is very helpful to set expectations about the course of the disease.

11.15.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.16 Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients

11.16.1 Keywords

- Lymphopenia
- Neutrophil to CD8 T cell ratio (N8R)

- inflammatory cytokines

11.16.2 Main Findings

Liu et al. enrolled a cohort of 40 patients from Wuhan including 27 mild cases and 13 severe cases of COVID-19. They performed a 16-day kinetic analysis of peripheral blood from time of disease onset. Patients in the severe group were older (medium age of 59.7, compared to 48.7 in mild group) and more likely to have hypertension as a co-morbidity. Lymphopenia was observed in 44.4% of the mild patients and 84.6% of the severe patients. Lymphopenia was due to low T cell count, specially CD8 T cells. Severe patients showed higher neutrophil counts and an increase of cytokines in the serum (IL2, IL6, IL10 and IFN γ). The authors measured several other clinical laboratory parameters were also higher in severe cases compared to mild, but concluded that neutrophil to CD8 T cell ratio (N8R) as the best prognostic factor to identify the severe cases compared to other receiver operating characteristic (ROC).

11.16.3 Limitations

This was a small cohort (N=40), and two of the patients initially included in the severe group (N=13) passed away and were excluded from the analysis due to lack of longitudinal data. However, it would be most important to be able to identify patients with severe disease with higher odds of dying. It seems that the different time points analyzed relate to hospital admission, which the authors describe as disease onset. The time between first symptoms and first data points is not described. It would have been important to analyze how the different measured parameters change according to health condition, and not just time (but that would require a larger cohort). The predictive value of N8R compared to the more commonly used NLR needs to be assessed in other independent and larger cohorts. Lastly, it is important to note that pneumonia was detected in patients included in the “mild” group, but according to the Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition) this group should be considered “moderate”.

11.16.4 Significance

Lymphopenia and cytokine storm have been described to be detrimental in many other infections including SARS-CoV1 and MERS-CoV. However, it was necessary to confirm that this dramatic immune response was also observed in the SARS-CoV2 infected patients. These results and further validation of the N8R ratio as a predictor of disease severity will contribute for the management of COVID19 patients and potential development of therapies.

11.16.5 Credit

Review by Pauline Hamon as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.17 Clinical and immunologic features in severe and moderate forms of Coronavirus Disease 2019

Chen et al. *medRxiv* [[592](#)]

11.17.1 Keywords

- severe disease
- lymphocytes
- cytokines

- IFN γ
- CD4 T cells
- HLA-DR CD8
- T cells

11.17.2 Main Findings

This study retrospectively evaluated clinical, laboratory, hematological, biochemical and immunologic data from 21 subjects admitted to the hospital in Wuhan, China (late December/January) with confirmed SARS-CoV-2 infection. The aim of the study was to compare 'severe' (n=11, ~64 years old) and 'moderate' (n=10, ~51 years old) COVID-19 cases. Disease severity was defined by patients' blood oxygen level and respiratory output. They were classified as 'severe' if SpO₂ 93% or respiratory rates 30 per min.

In terms of the clinical laboratory measures, 'severe' patients had higher CRP and ferritin, alanine and aspartate aminotransferases, and lactate dehydrogenase but lower albumin concentrations.

The authors then compared plasma cytokine levels (ELISA) and immune cell populations (PBMCs, Flow Cytometry). 'Severe' cases had higher levels of IL-2R, IL-10, TNF α , and IL-6 (marginally significant). For the immune cell counts, 'severe' group had higher neutrophils, HLA-DR⁺ CD8 T cells and total B cells; and lower total lymphocytes, CD4 and CD8 T cells (except for HLA-DR⁺), CD45RA Tregs, and IFN γ -expressing CD4 T cells. No significant differences were observed for IL-8, counts of NK cells, CD45+RO Tregs, IFN γ -expressing CD8 T and NK cells.

11.17.3 Limitations

Several potential limitations should be noted: 1) Blood samples were collected 2 days post hospital admission and no data on viral loads were available; 2) Most patients were administered medications (e.g. corticosteroids), which could have affected lymphocyte counts. Medications are briefly mentioned in the text of the manuscript; authors should include medications as part of Table 1. 3) 'Severe' cases were significantly older and 4/11 'severe' patients died within 20 days. Authors should consider a sensitivity analysis of biomarkers with the adjustment for patients' age.

11.17.4 Significance

Although the sample size was small, this paper presented a broad range of clinical, biochemical, and immunologic data on patients with COVID-19. One of the main findings is that SARS-CoV-2 may affect T lymphocytes, primarily CD4⁺ T cells, resulting in decreased IFN γ production. Potentially, diminished T lymphocytes and elevated cytokines can serve as biomarkers of severity of COVID-19.

11.17.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.18 SARS-CoV-2 and SARS-CoV Spike-RBD Structure and Receptor Binding Comparison and Potential Implications on Neutralizing Antibody and Vaccine Development

11.18.1 Keywords

- SARS-CoV
- SARS-CoV-2
- ACE2
- Spike (S) protein
- receptor binding domain (RBD)
- receptor binding motif (RBM)
- neutralizing antibody

11.18.2 Main Findings

This study compared the structure of SARS-CoV and SARS-CoV-2 Spike (S) protein receptor binding domain (RBD) and interactions with ACE2 using computational modeling, and interrogated cross-reactivity and cross-neutralization of SARS-CoV-2 by antibodies against SARS-CoV. While SARS-CoV and SARS-CoV-2 have over 70 % sequence homology and share the same human receptor ACE2, the receptor binding motif (RBM) is only 50% homologous.

Computational prediction of the SARS-CoV-2 and ACE2 interactions based on the previous crystal structure data of SARS-CoV, and measurement of binding affinities against human ACE2 using recombinant SARS-CoV and SARS-CoV-2 S1 peptides, demonstrated similar binding of the two S1 peptides to ACE2, explaining the similar transmissibility of SARS-CoV and SARS-CoV-2 and consistent with previous data (Wall et al Cell 2020).

The neutralization activity of SARS-CoV-specific rabbit polyclonal antibodies were about two-order of magnitude less efficient to neutralize SARS-CoV-2 than SARS-CoV, and four potentially neutralizing monoclonal antibodies against SARS-CoV had poor binding and neutralizing activity against SARS-CoV-2. In contrast, 3 poor SARS-CoV-binding monoclonal antibodies show some efficiency to bind and neutralize SARS-CoV-2. The results suggest that that antibodies to more conserved regions outside the RBM motif might possess better cross-protective neutralizing activities between two strains.

11.18.3 Limitations

It would have been helpful to show the epitopes recognized by the monoclonal antibodies tested on both SARS-CoV, SARS-CoV-2 to be able to make predictions for induction of broadly neutralizing antibodies. The data on monoclonal antibody competition with ACE2 for binding to SARS-CoV RBD should have also included binding on SARS-CoV2, especially for the three monoclonal antibodies that showed neutralization activity for SARS-CoV2. Because of the less homology in RBM sequences between viruses, it still may be possible that these antibodies would recognize the ACE2 RBD in SARS-CoV-2.

11.18.4 Significance

It is noteworthy that immunization to mice and rabbit with SARS-CoV S1 or RBD protein could induce monoclonal antibodies to cross-bind and cross-neutralize SARS-CoV-2 even if they are not ACE2-blocking. If these types of antibodies could be found in human survivors or in the asymptomatic populations as well, it might suggest that exposure to previous Coronavirus strains could have induced cross-neutralizing antibodies and resulted in the protection from severe symptoms in some cases of SARS-CoV2.

11.18.5 Credit

11.19 Protection of Rhesus Macaque from SARS-Coronavirus challenge by recombinant adenovirus vaccine

Chen et al. *bioRxiv* [[594](#)]

11.19.1 Keywords

- SARS-CoV-1
- rhesus macaque
- recombinant adenovirus vaccine

11.19.2 Main Findings

Rhesus macaques were immunized intramuscularly twice (week 0 and week 4) with SV8000 carrying the information to express a S1-orf8 fusion protein and the N protein from the BJ01 strain of SARS-CoV-1. By week 8, immunized animals had signs of immunological protection (IgG and neutralization titers) against SARS-CoV-1 and were protected against challenge with the PUMC-1 strain, with fewer detectable symptoms of respiratory distress, lower viral load, shorter periods of viral persistence, and less pathology in the lungs compared to non-immunized animals.

11.19.3 Limitations

The authors should write clearer descriptions of the methods used in this article. They do not describe how the IgG titers or neutralization titers were determined. There are some issues with the presentation of data, for example, in Figure 1a, y-axis should not be Vmax; forming cells and 1d would benefit from showing error bars. Furthermore, although I inferred that the animals were challenged at week 8, the authors did not explicitly detail when the animals were challenged. The authors should explain the design of their vaccine, including the choice of antigens and vector. The authors also do not include a description of the ethical use of animals in their study.

11.19.4 Significance

The authors describe a vaccine for SARS-CoV-1 with no discussion of possible implications for the current SARS-CoV-2 pandemic. Could a similar vaccine be designed to protect against SARS-CoV-2 and would the concerns regarding emerging viral mutations that the authors describe as a limitation for SARS-CoV-1 also be true in the context of SARS-CoV-2?

11.19.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.20 Reduction and Functional Exhaustion of T cells in Patients with Coronavirus Disease 2019 (COVID-19)

[[595](#)]

11.20.1 Keywords

- T cell exhaustion
- T cell lymphopenia
- IL-6
- IL-10
- TNF- α

11.20.2 Main Findings

Based on a retrospective study of 522 COVID patients and 40 healthy controls from two hospitals in Wuhan, China, authors show both age-dependent and clinical severity-dependent decrease in T cell numbers with elderly patients and patients who are in ICU-care showing the most dramatic decrease in T cell counts. Cytokine profiling of COVID patients reveal that TNF- α , IL-6 and IL-10 are increased in infected patients with patients in the ICU showing the highest levels. Interestingly, these three cytokine levels were inversely correlated with T cell counts and such inverse relationship was preserved throughout the disease progression. Surface staining of exhaustion markers (PD-1 and Tim-3) and flow cytometry of stained peripheral blood of 14 patients and 3 healthy volunteers demonstrate that T cells of COVID patients have increased expression of PD-1 with patients in ICU having the highest number of CD8⁺PD-1⁺ cells than their counterparts in non-ICU groups.

11.20.3 Limitations

Compared to the number of patients, number of control (n= 40) is small and is not controlled for age. Additional data linking inflammatory cytokines and the quality of the adaptive response including humoral and antigen specific T cell response is much needed. T cell exhaustion study relies on marker-dependent labeling of T cell functionality of a very limited sample size (n=17)—a functional/mechanistic study of these T cells from PBMCs would have bolstered their claims.

11.20.4 Significance

Limited but contains interesting implications. It is already known in literature that in the context of acute respiratory viral infections CD8 T cells exhibit exhaustion-like phenotypes which further underscores the importance of mechanistic studies that can elucidate how COVID infection leads to lymphopenia and T cell exhaustion-like phenotype.

However, as authors have noted, the data does point to an interesting question: How these inflammatory cytokines (TNF- α , IL-6 and IL-10) correlate with or affect effective viral immunity and what types of cells produce these cytokines? Answering that question will help us refine our targets for immune-modulatory therapies especially in patients suffering from cytokine storms.

11.20.5 Credit

This review by Chang Moon was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.21 Clinical Characteristics of 25 death cases infected with COVID-19 pneumonia: a retrospective review of medical records in a single medical center, Wuhan, China

[596]

11.21.1 Keywords

- COVID-19
- pneumonia
- hypertension
- diabetes
- biomarker
- neutrophilia
- lymphopenia

11.21.2 Main Findings

Most common chronic conditions among 25 patients that died from COVID-19 related respiratory failure were hypertension (64%) and diabetes (40%). Disease progression was marked by progressive organ failure, starting first with lung dysfunction, then heart (e.g. increased cTnl and pro-BNP), followed by kidney (e.g. increased BUN, Cr), and liver (e.g. ALT, AST). 72% of patients had neutrophilia and 88% also had lymphopenia. General markers of inflammation were also increased (e.g. PCT, D-Dimer, CRP, LDH, and SAA).

11.21.3 Limitations

The limitations of this study include small sample size and lack of measurements for some tests for several patients. This study would also have been stronger with comparison of the same measurements to patients suffering from less severe disease to further validate and correlate proposed biomarkers with disease severity.

11.21.4 Significance

This study identifies chronic conditions (i.e. hypertension and diabetes) that strongly correlates with disease severity. In addition to general markers of inflammation, the authors also identify concomitant neutrophilia and lymphopenia among their cohort of patients. This is a potentially interesting immunological finding because we would typically expect increased lymphocytes during a viral infection. Neutrophilia may also be contributing to cytokine storm. In addition, PCT was elevated in 90.5% of patients, suggesting a role for sepsis or secondary bacterial infection in COVID-19 related respiratory failure.

11.21.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.22 SARS-CoV-2 infection does not significantly cause acute renal injury: an analysis of 116 hospitalized patients with COVID-19 in a single hospital, Wuhan, China

[\[597\]](#)

11.22.1 Keywords

- CoVID-19
- 2019-nCoV
- SARS-CoV-2
- kidney
- clinical

- longitudinal

11.22.2 Main Findings

- Clinical data from 116 hospitalized CoVID-19 patients analyzed over 4 weeks for correlation with renal injury. Comorbidities included chronic renal failure (CRF) in 5 patients (4.3%).
- 10.8% of patients with no prior kidney disease showed elevations in blood urea or creatinine, and 7.2% of patients with no prior kidney disease showed albuminuria.
- Patients with pre-existing CRF underwent continuous renal replacement therapy (CRRT) alongside CoVID-19 treatment. Renal functions remained stable in these patients.
- All 5 patients with CRF survived CoVID-19 therapy without progression to ARDS or worsening of CRF.

11.22.3 Limitations

- Renal injury biomarkers in patients with incipient kidney abnormalities not tabulated separately, making overall data hard to interpret. It will be critical to separately examine kidney function (BUN, urine creatinine and eGFR) in patients that developed any kidney abnormalities (7.2~10.8% of cohort).
- No information on type of CoVID-19 therapy used across cohort; will be useful to correlate how treatment modality influences kidney function (and other parameters).
- Invokes previous clinical-correlation studies that indicate low instances of kidney damage[[598](#),[599](#)], but those studies did not track longitudinal urine samples for acute renal injury markers and viral shedding.
- CRRT in patients with CRF is standard therapy irrespective of CoVID-19 status; it will be important to compare clinical parameters of these patients (n=5) with virus-naïve CRF patients (none in this study) to make any meaningful conclusions.

11.22.4 Significance

- This study argues that renal impairment is uncommon in CoVID-19 and not associated with high mortality, in stark contrast with a concurrent study [[577](#)]. If supported by further studies, this argues kidney impairment is secondary to cytokine storm/inflammation-induced organ failure, and not due to direct viral replication.
- Will be important to comprehensively characterize large-datasets of CoVID-19 patients to conclude if kidney function actively disrupted due to viral infection.

11.22.5 Credit

Review by Samarth Hegde as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.23 Potential T-cell and B-Cell Epitopes of 2019-nCoV

11.23.1 Keywords

- COVID-19
- vaccine
- epitopes
- spike protein
- MHC-I
- MHC-II
- neutralizing antibodies
- ACE2

11.23.2 Main Findings

The authors use 2 neural network algorithms, NetMHCpan4 and MARIA, to identify regions within the COVID-19 genome that are presentable by HLA. They identify 405 viral epitopes that are presentable on MHC-I and MHC-II and validate using known epitopes from SARS-CoV. To determine whether immune surveillance drives viral mutations to evade MHC presentation, the authors analyzed 68 viral genomes from 4 continents. They identified 93 point mutations that occurred preferentially in regions predicted to be presented by MHC-I ($p=0.02$) suggesting viral evolution to evade CD8 T-cell mediated killing. 2 nonsense mutations were also identified that resulted in loss of presentation of an associated antigen (FGDSVEEVV) predicted to be good antigen for presentation across multiple HLA alleles.

To identify potential sites of neutralizing antibody binding, the authors used homology modeling to the SARS-CoV's spike protein (S protein) to determine the putative structure of the CoV2 spike protein. They used Discotope2 to identify antibody binding sites on the protein surface in both the down and up conformations of the S protein. The authors validate this approach by first identifying antibody binding site in SARS-CoV S protein. In both the down and up conformation of the CoV2 S protein, the authors identified a potential antibody binding site on the S protein receptor binding domain (RBD) of the ACE2 receptor (residues 440-460, 494-506). While RBDs in both SARS-CoV and CoV2 spike proteins may be important for antibody binding, the authors note that SARS-CoV has larger attack surfaces than CoV2. These results were later validated on published crystal structures of the CoV2 S protein RBD and human ACE2. Furthermore, analysis of 68 viral genomes did not identify any mutations in this potential antibody binding site in CoV2.

Finally, the authors compile a list of potential peptide vaccine candidates across the viral genome that can be presented by multiple HLA alleles. Several of the peptides showed homology to SARS-CoV T-cell and B-cell epitopes.

11.23.3 Limitations

While the authors used computational methods of validation, primarily through multiple comparisons to published SARS-CoV structures and epitopes, future work should include experimental validation of putative T-cell and B-cell epitopes.

11.23.4 Significance

The authors identified potential T-cell and B-cell epitopes that may be good candidates for peptide based vaccines against CoV2. They also made interesting observations in comparing SARS-CoV and CoV2 potential antibody binding sites, noting that SARS-CoV had larger attack surfaces for potential neutralizing antibody binding. One of the highlights of this paper was the authors' mutation analysis of 68 viral genomes from 4 continents. This analysis not only validated their computational method for identifying T-cell epitopes, but showed that immune surveillance likely drives viral mutation in

MHC-I binding peptides. The smaller attack surface may point to potential mechanisms of immune evasion by CoV2. However, absence of mutations in the RBD of CoV2 and the small number of mutations in peptides presentable to T cells suggests that vaccines against multiple epitopes could still elicit robust immunity against CoV2.

11.23.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.24 Structure, Function, and Antigenicity of the SARSCoV-2 Spike Glycoprotein

Walls et al. *bioRxiv*. [[601](#)] now [[46](#)]

11.24.1 Keywords

- binding affinity
- antigenicity
- neutralizing antibody

11.24.2 Main Findings

The authors highlight a human angiotensin-converting enzyme 2 (hACE2), as a potential receptor used by the current Severe Acute respiratory syndrome coronavirus-2 (SARS-CoV-2) as a host factor that allows the virus target human cells. This virus-host interaction facilitates the infection of human cells with a high affinity comparable with SARS-CoV. The authors propose this mechanism as a probable explanation of the efficient transmission of SARS-CoV-2 between humans. Besides, Walls and colleagues described SARS-CoV-2 S glycoprotein S by Cryo-EM along with neutralizing polyclonal response against SAR-CoV-2 S from mice immunized with SAR-CoV and blocking SAR-CoV-2 S-mediated entry into VeroE6 infected cells.**

11.24.3 Limitations

The SARS-CoV-2 depends on the cell factors ACE2 and TMPRSS2, this last, according to a recent manuscript by Markus Hoffman et al., *Cell*, 2020. The authors used green monkey (VeroE6) and hamster (BHK) cell lines in the experiments to drive its conclusions to humans; however, it is well known the caucasian colon adenocarcinoma human cell line (CaCo-2), highly express the hACE2 receptor as the TMPRSS2 protease as well. In humans, ACE2 protein is highly expressed in the gastrointestinal tract, which again, makes the CaCo-2 cell line suitable for the following SARS-CoV-2 studies.

11.24.4 Significance

The results propose a functional receptor used by SARS-CoV-2 to infect humans worldwide and defining two distinct conformations of spike (S) glycoprotein by cryogenic electron microscopy (Cryo-EM). This study might help establish a precedent for initial drug design and treatment of the current global human coronavirus epidemic.

11.24.5 Credit

11.25 Breadth of concomitant immune responses underpinning viral clearance and patient recovery in a non-severe case of COVID-19

Thevarajan et al. *medRxiv* [[602](#)]

11.25.1 Keywords

- IgG
- IgM
- Tfh cells
- NK cells
- SNP

11.25.2 Main Findings

The authors characterized the immune response in peripheral blood of a 47-year old COVID-19 patient.

SARS-CoV2 was detected in nasopharyngeal swab, sputum and faeces samples, but not in urine, rectal swab, whole blood or throat swab. 7 days after symptom onset, the nasopharyngeal swab test turned negative, at day 10 the radiography infiltrates were cleared and at day 13 the patient became asymptomatic.

Immunofluorescence staining shows from day 7 the presence of **COVID-19-binding IgG and IgM** antibodies in plasma, that increase until day 20.

Flow cytometry on whole blood reveals a plasmablast peak at day 8, a gradual increase in T follicular helper cells, stable HLA-DR⁺ NK frequencies and decreased monocyte frequencies compared to healthy counterparts. The expression of CD38 and HLA-DR peaked on T cells at D9 and was associated with higher production of cytotoxic mediators by CD8⁺ T cells.

IL-6 and IL-8 were undetectable in plasma.

The authors further highlight the presence of the **IFITM3 SNP-rs12252-C/C variant** in this patient, which is associated with higher susceptibility to influenza virus.

11.25.3 Limitations

These results need to be confirmed in additional patients.

COVID-19 patients have increased infiltration of macrophages in their lungs [[603](#)]. Monitoring monocyte proportions in blood earlier in the disease might help to evaluate their eventual migration to the lungs.

The stable concentration of HLA-DR⁺ NK cells in blood from day 7 is not sufficient to rule out NK cell activation upon SARS-CoV2 infection. In response to influenza A virus, NK cells express higher levels of activation markers CD69 and CD38, proliferate better and display higher cytotoxicity [[604](#)]. Assessing these parameters in COVID-19 patients is required to better understand NK cell role in clearing this infection.

Neutralization potential of the COVID-19-binding IgG and IgM antibodies should be assessed in future studies.

This patient was able to clear the virus, while presenting a SNP associated with severe outcome following influenza infection. The association between this SNP and outcome upon SARS-CoV2 infection should be further investigated.

11.25.4 Significance

This study is among the first to describe the appearance of COVID-19-binding IgG and IgM antibodies upon infection. The emergence of new serological assays might contribute to monitor more precisely the seroconversion kinetics of COVID-19 patients [242]. Further association studies between IFITM3 SNP-rs12252-C/C variant and clinical data might help to refine the COVID-19 outcome prediction tools.

11.25.5 Credit

Review by Bérengère Salomé as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.26 The landscape of lung bronchoalveolar immune cells in COVID-19 revealed by single-cell RNA sequencing

Liao et al. *medRxiv* [603]

11.26.1 Keywords

- COVID-19
- SARS-CoV-2
- Broncho-alveolar lavage
- macrophages
- NK cells
- T cells
- cytokine storm
- scRNAseq

11.26.2 Main Findings

The authors performed single-cell RNA sequencing (scRNAseq) on bronchoalveolar lavage fluid (BAL) from 6 COVID-19 patients (n=3 mild cases, n=3 severe cases). Data was compared to previously generated scRNAseq data from healthy donor lung tissue (n=8).

Clustering analysis of the 6 patients revealed distinct immune cell organization between mild and severe disease. Specifically, they found that transcriptional clusters annotated as tissue resident alveolar macrophages were strongly reduced while monocytes-derived FCN1⁺SPP1⁺ inflammatory macrophages dominated the BAL of patients with severe COVID19 diseases. They show that inflammatory macrophages upregulated interferon-signaling genes, monocytes recruiting chemokines including CCL2, CCL3, CCL4 as well as IL-6, TNF, IL-8 and profibrotic cytokine TGF-β, while alveolar macrophages expressed lipid metabolism genes, such as PPARG.

The lymphoid compartment was overall enriched in lungs from patients. Clonally expanded CD8 T cells were enriched in mild cases suggesting that CD8 T cells contribute to viral clearance as in Flu infection, whereas proliferating T cells were enriched in severe cases.

SARS-CoV-2 viral transcripts were detected in severe patients, but considered here as ambient contaminations.

11.26.3 Limitations

These results are based on samples from 6 patients and should therefore be confirmed in the future in additional patients. Longitudinal monitoring of BAL during disease progression or resolution would have been most useful.

The mechanisms underlying the skewing of the macrophage compartment in patients towards inflammatory macrophages should be investigated in future studies.

Deeper characterization of the lymphoid subsets is required. The composition of the “proliferating” cluster and how these cells differ from conventional T cell clusters should be assessed. NK and CD8 T cell transcriptomic profile, in particular the expression of cytotoxic mediator and immune checkpoint transcripts, should be compared between healthy and diseased lesions.

11.26.4 Significance

COVID-19 induces a robust inflammatory cytokine storm in patients that contributes to severe lung tissue damage and ARDS [605]. Accumulation of monocyte-derived inflammatory macrophages at the expense of Alveolar macrophages known to play an anti-inflammatory role following respiratory viral infection, in part through the PPAR γ pathway [606,607] are likely contributing to lung tissue injuries. These data suggest that reduction of monocyte accumulation in the lung tissues could help modulate COVID-19-induced inflammation. Further analysis of lymphoid subsets is required to understand the contribution of adaptive immunity to disease outcome.

11.26.5 Credit

Review by Bérengère Salomé and Assaf Magen as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.27 Can routine laboratory tests discriminate 2019 novel coronavirus infected pneumonia from other community-acquired pneumonia?

Pan et al. *medRxiv* [608]

11.27.1 Keywords

- Routine laboratory testing

11.27.2 Main Findings

In an attempt to use standard laboratory testing for the discrimination between “Novel Coronavirus Infected Pneumonia” (NCIP) and a usual community acquired pneumonia (CAP), the authors compared laboratory testing results of 84 NCIP patients with those of a historical group of 316 CAP patients from 2018 naturally COVID-19 negative. The authors describe significantly lower white blood- as well as red blood- and platelet counts in NCIP patients. When analyzing differential blood counts, lower absolute counts were measured in all subsets of NCIP patients. With regard to clinical chemistry parameters, they found increased AST and bilirubin in NCIP patients as compared to CAP patients.

11.27.3 Limitations

The authors claim to describe a simple method to rapidly assess a pre-test probability for NCIP. However, the study has substantial weakpoints. The deviation in clinical laboratory values in NCIP patients described here can usually be observed in severely ill patients. The authors do not comment on how severely ill the patients tested here were in comparison to the historical control. Thus, the conclusion that the tests discriminate between CAP and NCIP lacks justification.

11.27.4 Significance

The article strives to compare initial laboratory testing results in patients with COVID-19 pneumonia as compared to patients with a usual community acquired pneumonia. The implications of this study for the current clinical situation seem restricted due to a lack in clinical information and the use of a control group that might not be appropriate.

11.27.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.28 Correlation Analysis Between Disease Severity and Inflammation-related Parameters in Patients with COVID-19 Pneumonia

[609]

11.28.1 Keywords

- cytokine
- COVID-19 pneumonia
- severity
- disease progression

11.28.2 Main Findings

This study is a cross-sectional analysis of 100 patients with COVID-19 pneumonia, divided into mild (n = 34), severe (n = 34), and critical (n = 32) disease status based on clinical definitions.

The criteria used to define disease severity are as follows:

1. *Severe* – any of the following: respiratory distress or respiratory rate ≥ 30 respirations/minute; oxygen saturation $\leq 93\%$ at rest; oxygen partial pressure (PaO₂)/oxygen concentration (FiO₂) in arterial blood ≤ 300 mmHg, progression of disease on imaging to $>50\%$ lung involvement in the short term.
2. *Critical* – any of the following: respiratory failure that requires mechanical ventilation; shock; other organ failure that requires treatment in the ICU.
3. Patients with pneumonia who test positive for COVID-19 who do not have the symptoms delineated above are considered *mild*.

Peripheral blood inflammatory markers were correlated to disease status. Disease severity was significantly associated with levels of IL-2R, IL-6, IL-8, IL-10, TNF- α , CRP, ferroprotein, and procalcitonin. Total WBC count, lymphocyte count, neutrophil count, and eosinophil count were also significantly correlated with disease status. Since this is a retrospective, cross-sectional study of clinical laboratory

values, these data may be extrapolated for clinical decision making, but without studies of underlying cellular causes of these changes this study does not contribute to a deeper understanding of SARS-CoV-2 interactions with the immune system.

It is also notable that the mean age of patients in the mild group was significantly different from the mean ages of patients designated as severe or critical ($p < 0.001$). The mean patient age was not significantly different between the severe and critical groups. However, IL-6, IL-8, procalcitonin (Table 2), CRP, ferroprotein (Figure 3A, 3B), WBC count, and neutrophil count (Figure 4A, 4B) were all significantly elevated in the critical group compared to severe. These data suggest underlying differences in COVID-19 progression that is unrelated to age.

11.28.3 Significance

Given the inflammatory profile outlined in this study, patients who have mild or severe COVID-19 pneumonia, who *also* have any elevations in the inflammatory biomarkers listed above, should be closely monitored for potential progression to critical status.

11.28.4 Credit

This review by JJF was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.29 An Effective CTL Peptide Vaccine for Ebola Zaire Based on Survivors' CD8+ Targeting of a Particular Nucleocapsid Protein Epitope with Potential Implications for COVID-19 Vaccine Design

Herst et al. *bioRxiv* [[610](#)]

11.29.1 Keywords

- Peptide vaccine
- Ebolavirus
- nucleocapsid
- epitope
- vaccine design
- microsphere

11.29.2 Main Findings

Vaccination of mice with a single dose of a 9-amino-acid peptide NP44-52 located in a conserved region of ebolavirus (EBOV) nucleocapsid protein (NP) confers CD8+ T-cell-mediated immunity against mouse adapted EBOV (maEBOV). Bioinformatic analyses predict multiple conserved CD8+ T cell epitopes in the SARS-CoV-2 NP, suggesting that a similar approach may be feasible for vaccine design against SARS-CoV-2.

The authors focus on a site within a 20-peptide region of EBOV NP which was commonly targeted by CD8+ T cells in a group of EBOV survivors carrying the HLA-A*30:01:01 allele. To justify the testing of specific vaccine epitopes in a mouse challenge setting, the authors cite known examples of human pathogen-derived peptide antigens that are also recognized by C57BL/6 mice, as well as existing data surrounding known mouse immunogenicity of peptides related to this EBOV NP region. Testing 3 distinct 9mer peptides over an 11 amino-acid window and comparing to vaccination with the 11mer

with a T-cell reactivity readout demonstrated that optimizing peptide length and position for immunogenicity may be crucial, likely due to suboptimal peptide processing and MHC-class-I loading.

Vaccines for maEBOV challenge studies were constructed by packaging NP44-52 in d,l poly(lactic-co-glycolic) acid microspheres. CpG was also packaged within the microspheres, while Monophosphoryl Lipid A (a TLR4 ligand) was added to the injectate solution. A second peptide consisting of a predicted MHC-II epitope from the EBOV VG19 protein was added using a separate population of microspheres, and the formulation was injected by intraperitoneal administration. The vaccine was protective against a range of maEBOV doses up to at least 10,000 PFU. Survival was anticorrelated with levels of IL6, MCP-1 (CCL2), IL9, and GM-CSF, which recapitulated trends seen in human EBOV infection.

While HLA-A*30:01:01 is only present in a minority of humans, the authors state that MHC binding algorithms predict NP44-52 to be a strong binder of a set of more common HLA-A*02 alleles. The authors predict that a peptide vaccine based on the proposed formulation could elicit responses in up to 50% of people in Sudan or 30% of people in North America.

SARS-CoV-2 NP, meanwhile, has conserved regions which may provide peptide-vaccine candidates. Scanning the SARS-CoV-2 NP sequence for HLA-binding 9mers identified 53 peptides with predicted binding affinity < 500nM, including peptides that are predicted to bind to HLA-class-I alleles of 97% of humans, 7 of which have previously been tested *in-vitro*.

The results support previously appreciated correlations between certain cytokines and disease severity, specifically IL6 which relates to multiple trial therapies. Prediction of HLA-class-I binding of SARS-CoV-2 NP peptides suggests the plausibility of a peptide vaccine targeting conserved regions of SARS-CoV-2 NP although further validation in previously infected patient samples will be essential.

11.29.3 Credit

Review by Andrew M. Leader as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.30 Epitope-based peptide vaccines predicted against novel coronavirus disease caused by SARS-CoV-2

Li et al. *bioRxiv*. [[611](#)]

11.30.1 Keywords

- SARS-CoV-2
- immune-informatics
- vaccine design
- T cell epitope
- B cell epitope

11.30.2 Main Findings

This study employs a series of bioinformatic pipelines to identify T and B cell epitopes on spike (S) protein of SARS-CoV-2 and assess their properties for vaccine potential. To identify B cell epitopes, they assessed structural accessibility, hydrophilicity, and beta-turn and flexibility which are all factors that promote their targeting by antibodies. To identify T cell epitopes, they filtered for peptides with high antigenicity score and capacity to bind 3 or more MHC alleles. Using the protein digest server, they also demonstrated that their identified T and B cell epitopes are stable, having multiple non-

digesting enzymes per epitope. Epitopes were also determined to be non-allergenic and non-toxin as assessed by Allergen FP 1.0 and ToxinPred, respectively. For T cell epitopes, they assessed the strength of epitope-HLA interaction via PepSite. Overall, they predict four B cell and eleven T cell epitopes (two MHC I and nine MHC II binding) to pass stringent computational thresholds as candidates for vaccine development. Furthermore, they performed sequence alignment between all identified SARS-CoV-2 S protein mutations and predicted epitopes, and showed that the epitopes are conserved across 134 isolates from 38 locations worldwide. However, they report that these conserved epitopes may soon become obsolete given the known mutation rate of related SARS-CoV is estimated to be 4×10^{-4} /site/year, underscoring the urgency of anti-viral vaccine development.

11.30.3 Limitations

While spike (S) protein may have a critical role in viral entry into host cells and their epitope prediction criterion were comprehensive, this study did not examine other candidate SARS-CoV-2 proteins. This point is particularly important given that a single epitope may not be sufficient to induce robust immune memory, and recent approaches involve multi-epitope vaccine design. Furthermore, their study only included a direct implementation of various published methods, but did not validate individual bioinformatic tools with controls to demonstrate robustness. Finally, it is critical that these predicted epitopes are experimentally validated before any conclusions can be drawn about their potential as vaccine candidates or their clinical efficacy.

11.30.4 Significance

This study provides a computational framework to rapidly identify epitopes that may serve as potential vaccine candidates for treating SARS-CoV-2.

11.30.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.31 The definition and risks of Cytokine Release Syndrome-Like in 11 COVID-19-Infected Pneumonia critically ill patients: Disease Characteristics and Retrospective Analysis

Wang Jr. et al. *medRxiv*. [[612](#)]

11.31.1 Keywords

- Cytokine release syndrome (CRS)
- biomarkers
- ARDS
- IL-6
- lymphopenia

11.31.2 Main Findings

This study describes the occurrence of a cytokine release syndrome-like (CRSL) toxicity in ICU patients with COVID-19 pneumonia. The median time from first symptom to acute respiratory distress syndrome (ARDS) was 10 days. All patients had decreased CD3, CD4 and CD8 cells, and a significant increase of serum IL-6. Furthermore, 91% had decreased NK cells. The changes in IL-6 levels preceded those in CD4 and CD8 cell counts. All of these parameters correlated with the area of pulmonary

inflammation in CT scan images. Mechanical ventilation increased the numbers of CD4 and CD8 cells, while decreasing the levels of IL-6, and improving the immunological parameters.

11.31.3 Limitations

The number of patients included in this retrospective single center study is small (n=11), and the follow-up period very short (25 days). Eight of the eleven patients were described as having CRS, and were treated by intubation (7) or ECMO (2). Nine patients were still in the intensive care unit at the time of publication of this article, so their disease outcome is unknown.

11.31.4 Significance

The authors define a cytokine release syndrome-like toxicity in patients with COVID-19 with clinical radiological and immunological criteria: 1) decrease of circulating CD4, CD8 and NK cells; 2) substantial increase of IL-6 in peripheral blood; 3) continuous fever; 4) organ and tissue damage. This event seems to occur very often in critically ill patients with COVID-19 pneumonia. Interestingly, the increase of IL-6 in the peripheral blood preceded other laboratory alterations, thus, IL-6 might be an early biomarker for the severity of COVID-19 pneumonia. The manuscript will require considerable editing for organization and clarity.

11.31.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.32 Clinical characteristics of 36 non-survivors with COVID-19 in Wuhan, China

Huang et al. *medRxiv*. [[613](#)]

11.32.1 Keywords

- Clinical Characteristics
- Non Survivors
- retrospective study

11.32.2 Main Findings

This is a simple study reporting clinical characteristics of patients who did not survive COVID-19. All patients (mean age=69.22 years) had acute respiratory distress syndrome (ARDS) and their median time from onset to ARDS was 11 days. The median time from onset to death was 17 days. Most patients were older male (70% male) with co-morbidities and only 11 % were smokers. 75% patients showed bilateral pneumonia. Many patients had chronic diseases, including hypertension (58.33%), cardiovascular disease (22.22%) and diabetes (19.44%). Typical clinical feature measured in these patients includes lymphopenia and elevated markers of inflammation.

11.32.3 Limitations

As noted by the authors, the conclusions of this study are very limited because this is single-centered study focusing on a small cohort of patients who did not survive. Many clinical parameters observed by the authors (such* as increase levels of serum CRP, PCT, IL-6) have also been described in other COVID19 patients who survived the infection

11.32.4 Significance

This study is essentially descriptive and may be useful for clinical teams monitoring COVID19 patients.

11.32.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.33 Risk Factors Related to Hepatic Injury in Patients with Corona Virus Disease 2019

[614]

11.33.1 Keywords

- COVID-related Hepatic Injury

11.33.2 Main Findings

Based on a retrospective study of 85 hospitalized COVID patients in a Beijing hospital, authors showed that patients with elevated ALT levels ($n = 33$) were characterized by significantly higher levels of lactic acid and CRP as well as lymphopenia and hypoalbuminemia compared to their counterparts with normal ALT levels. Proportion of severe and critical patients in the ALT elevation group was significantly higher than that of normal ALT group. Multivariate logistic regression performed on clinical factors related to ALT elevation showed that $\text{CRP} \geq 20\text{mg/L}$ and low lymphocyte count ($<1.1 \times 10^9$ cells/L) were independently related to ALT elevation—a finding that led the authors to suggest cytokine storm as a major mechanism of liver damage.

11.33.3 Limitations

The article's most attractive claim that liver damage seen in COVID patients is caused by cytokine storm (rather than direct infection of the liver) hinges solely on their multivariate regression analysis. Without further mechanistic studies a) demonstrating how high levels of inflammatory cytokines can induce liver damage and b) contrasting types of liver damage incurred by direct infection of the liver vs. system-wide elevation of inflammatory cytokines, their claim remains thin. It is also worth noting that six of their elevated ALT group ($n=33$) had a history of liver disease (i.e. HBV infection, alcoholic liver disease, fatty liver) which can confound their effort to pin down the cause of hepatic injury to COVID.

11.33.4 Significance

Limited. This article confirms a rich body of literature describing liver damage and lymphopenia in COVID patients.

11.33.5 Credit

Review by Chang Moon as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.34 Detectable serum SARS-CoV-2 viral load (RNAemia) is closely associated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients

[615]

11.34.1 Keywords

- ARDS
- interleukin-6 (IL-6)
- procalcitonin (PCT)
- pro-inflammatory cytokines
- SARS-CoV-2 RNAemia

11.34.2 Main Findings

48 adult patients diagnosed with Covid19 according to Chinese guidelines for Covid19 diagnosis and treatment version 6 were included in this study. Patients were further sub-divided into three groups based on clinical symptoms and disease severity: (1) mild, positive Covid19 qPCR with no or mild clinical symptoms (fever; respiratory; radiological abnormalities); (2) severe, at least one of the following: shortness of breath/respiratory rate $>30/\text{min}$, oxygen saturation $\text{SaO}_2 < 93\%$, Horowitz index $\text{paO}_2/\text{FiO}_2 < 300 \text{ mmHg}$ (indicating moderate pulmonary damage); and (3) critically ill, at least one additional complicating factor: respiratory failure with need for mechanical ventilation; systemic shock; multi-organ failure and transfer to ICU. Serum samples and throat-swabs were collected from all 48 patients enrolled. SARS-CoV-2 RNA was assessed by qPCR with positive results being defined as Ct values < 40 , and serum interleukin-6 (IL-6) was quantified using a commercially available detection kit. Briefly, patient characteristics in this study confirm previous reports suggesting that higher age and comorbidities are significant risk factors of clinical severity. Of note, 5 out of 48 of patients (10.41%), all in the critically ill category, were found to have detectable serum SARS-CoV-2 RNA levels, so-called RNAemia. Moreover, serum IL-6 levels in these patients were found to be substantially higher and this correlated with the presence of detectable SARS-CoV-2 RNA levels. The authors hypothesize that viral RNA might be released from acutely damages tissues in moribund patients during the course of Covid19 and that RNAemia along with IL-6 could potentially be used as a prognostic marker.

11.34.3 Limitations

While this group's report generally confirms some of the major findings of a more extensive study, published in early February 2020, [605], there are limitations that should be taken into account. First, the number of patients enrolled is relatively small; second, interpretation of these data would benefit from inclusion of information about study specifics as well as providing relevant data on the clinical course of these patients other than the fact that some were admitted to ICU (i.e. demographics on how many patients needed respiratory support, dialysis, APACHE II/III or other standard ICU scores as robust prognostic markers for mortality etc). It also remains unclear at which time point the serum samples were taken, i.e. whether at admission, when the diagnosis was made or during the course of the hospital stay (and potentially after onset of therapy, which could have affected both IL-6 and RNA levels). The methods section lacks important information on the qPCR protocol employed, including primers and cycling conditions used. From a technical point of view, Ct values >35 seem somewhat non-specific (although Ct <40 was defined as the CDC cutoff as well) indicating that serum RNA levels are probably very low, therefore stressing the need for highly specific primers and high qPCR efficiency. In addition, the statistical tests used (t-tests, according to the methods section) do not seem appropriate as the organ-specific data such as BUN and troponin T values seem to be not normally

distributed across groups (n= 5 RNAemia+ vs. n= 43 RNAemia-). Given the range of standard deviations and the differences in patient sample size, it is difficult to believe that these data are statistically significantly different.

11.34.4 Significance

This study is very rudimentary and lacks a lot of relevant clinical details. However, it corroborates some previously published observations regarding RNAemia and IL-6 by another group. Generally, regarding future studies, it would be important to address the question of IL-6 and other inflammatory cytokine dynamics in relation to Covid19 disease kinetics (high levels of IL-6, IL-8 and plasma leukotriene were shown to have prognostic value at the onset of ARDS ; serum IL-2 and IL-15 have been associated with mortality; reviewed by Chen W & Ware L, Clin Transl Med. 2015 [[616](#)]).

11.34.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.35 Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study

[[617](#)]

11.35.1 Keywords

- Lymphopenia

11.35.2 Main Findings

Based on a retrospective study of 162 COVID patients from a local hospital in Wuhan, China, the authors show an inverse correlation between lymphocyte % (LYM%) of patients and their disease severity. The authors have also tracked LYM% of 70 cases (15 deaths; 15 severe; 40 moderate) throughout the disease progression with fatal cases showing no recovery of lymphocytes (<5%) even after 17-19 days post-onset. The temporal data of LYM % in COVID patients was used to construct a Time-Lymphocyte% model which is used to categorize and predict patients' disease severity and progression. The model was validated using 92 hospitalized cases and kappa statistic test was used to assess agreement between predicted disease severity and the assigned clinical severity (k = 0.49).

11.35.3 Limitations

Time-Lymphocyte % Model (TLM) that authors have proposed as a predictive model for clinical severity is very simple in its construction and derives from correlative data of 162 patients. In order for the model to be of use, it needs validation using a far more robust data set and possibly a mechanistic study on how COVID leads to lymphopenia in the first place. In addition, it should be noted that no statistical test assessing significance of LYM % values between disease severities was performed.

11.35.4 Significance

This article is of limited significance as it simply reports similar descriptions of COVID patients made in previous literature that severe cases are characterized by lymphopenia.

11.35.5 Credit

Review by Chang Moon as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.36 The potential role of IL-6 in monitoring severe case of coronavirus disease 2019

Liu et al. *medRxiv*. [[618](#)]

11.36.1 Keywords

- Cytokine Release Syndrome
- lymphocytopenia
- IL-6
- CRP
- COVID19
- pneumonia

11.36.2 Main Findings

Study on blood biomarkers on 80 COVID19 patients (69 severe and 11 non-severe). Patients with severe symptoms at admission (baseline) showed obvious lymphocytopenia and significantly increased interleukin-6 (IL-6) and CRP, which was positively correlated with symptoms severity. IL-6 at baseline positively correlates with CRP, LDH, ferritin and D-Dimer abundance in blood.

Longitudinal analysis of 30 patients (before and after treatment) showed significant reduction of IL-6 in remission cases.

11.36.3 Limitations

Limited sample size at baseline, especially for the non-severe leads to question on representativeness. The longitudinal study method is not described in detail and suffers from non-standardized treatment. Limited panel of pro-inflammatory cytokine was analyzed. Patients with severe disease show a wide range of altered blood composition and biomarkers of inflammation, as well as differences in disease course (53.6% were cured, about 10% developed acute respiratory distress syndrome). The authors comment on associations between IL-6 levels and outcomes, but these were not statistically significant (maybe due to the number of patients, non-standardized treatments, etc.) and data is not shown. Prognostic biomarkers could have been better explored. Study lacks multivariate analysis.

11.36.4 Significance

IL-6 could be used as a pharmacodynamic marker of disease severity. Cytokine Release Syndrome (CRS) is a well-known side effect for CAR-T cancer therapy and there are several effective drugs to manage CRS. Drugs used to manage CRS could be tested to treat the most severe cases of COVID19.

11.36.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.37 Clinical and Laboratory Profiles of 75 Hospitalized Patients with Novel Coronavirus Disease 2019 in Hefei, China

Zhao et al. *medRxiv*. [[619](#)]

11.37.1 Keywords

- Routine laboratory testing

11.37.2 Main Findings

The authors of this study provide a comprehensive analysis of clinical laboratory assessments in 75 patients (median age 47 year old) hospitalized for Corona virus infection in China measuring differential blood counts including T-cell subsets (CD4, CD8), coagulation function, basic blood chemistry, of infection-related biomarkers including CRP, Procalcitonin (PCT) (Precursor of calcitonin that increases during bacterial infection or tissue injury), IL-6 and erythrocyte sedimentation rate as well as clinical parameters. Among the most common hematological changes they found increased neutrophils, reduced CD4 and CD8 lymphocytes, increased LDH, CRP and PCT

When looking at patients with elevated IL-6, the authors describe significantly reduced CD4 and CD8 lymphocyte counts and elevated CRP and PCT levels were significantly increased in infected patients suggesting that increased IL-6 may correlate well with disease severity in COVID-19 infections

11.37.3 Limitations

The authors performed an early assessment of clinical standard parameters in patients infected with COVID-19. Overall, the number of cases (75) is rather low and the snapshot approach does not inform about dynamics and thus potential relevance in the assessment of treatment options in this group of patients.

11.37.4 Significance

The article summarizes provides a good summary of some of the common changes in immune cells inflammatory cytokines in patients with a COVID-19 infection and. Understanding how these changes can help predict severity of disease and guide therapy including IL-6 cytokine receptor blockade using Tocilizumab or Sarilumab will be important to explore.

11.37.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.38 Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome

Yang et al. *medRxiv* [[620](#)]

11.38.1 Keywords

- cytokine
- IP-10

- MCP-3
- IL-1Ra
- lymphocyte
- neutrophil
- stratification
- disease severity
- viral load
- lung function
- complications
- clinical data

11.38.2 Summary

Plasma cytokine analysis (48 cytokines) was performed on COVID-19 patient plasma samples, who were sub-stratified as severe (N=34), moderate (N=19), and compared to healthy controls (N=8). Patients were monitored for up to 24 days after illness onset: viral load (qRT-PCR), cytokine (multiplex on subset of patients), lab tests, and epidemiological/clinical characteristics of patients were reported.

11.38.3 Main Findings

- Many elevated cytokines with COVID-19 onset compared to healthy controls (IFN γ , IL-1Ra, IL-2Ra, IL-6, IL-10, IL-18, HGF, MCP-3, MIG, M-CSF, G-CSF, MIG-1a, and IP-10).
- IP-10, IL-1Ra, and MCP-3 (esp. together) were associated with disease severity and fatal outcome.
- IP-10 was correlated to patient viral load ($r=0.3006$, $p=0.0075$).
- IP-10, IL-1Ra, and MCP-3 were correlated to loss of lung function (PaO₂/FaO₂ (arterial/atmospheric O₂) and Murray Score (lung injury) with MCP-3 being the most correlated ($r=0.4104$ $p<0.0001$ and $r=0.5107$ $p<0.0001$ respectively).
- Viral load (Lower Ct Value from qRT-PCR) was associated with upregulated IP-10 only (not IL-1Ra or MCP-3) and was mildly correlated with decreased lung function: PaO₂/FaO₂ (arterial/atmospheric O₂) and Murray Score (lung injury).
- Lymphopenia (decreased CD4 and CD8 T cells) and increased neutrophil correlated w/ severe patients.
- Complications were associated with COVID severity (ARDS, hepatic insufficiency, renal insufficiency).

11.38.4 Limitations

Collection time of clinical data and lab results not reported directly (likely 4 days (2,6) after illness onset), making it very difficult to determine if cytokines were predictive of patient outcome or reflective of patient compensatory immune response (likely the latter). Small N for cytokine analysis (N=2 fatal and N=5 severe/critical, and N=7 moderate or discharged). Viral treatment strategy not clearly outlined.

11.38.5 Expanded Results

NOTE: Moderate COVID-19 was classified by fever, respiratory manifestations, and radiological findings consistent with pneumonia while severe patients had one or more of the following: 1)

respiratory distraction, resting O₂ saturation, or 3) arterial PaO₂/FiO₂ < 300 mmHg.

Cytokine Results (Human Cytokine Screening Panel, Bio-Rad):

- **Significant elevation of cytokines observed in COVID patients compared to healthy controls: IFN γ , IL-1Ra, IL-2Ra, IL-6, IL-10, IL-18, HGF, MCP-3, MIG, M-CSF, G-CSF, MIG-1a, and IP-10.**
- Severity was correlated **with increase in measured IP-10, MCP-3, and IL-Ra** as measure by area under the curve analysis during sample timecourse (2-24 days after illness onset).
- IL-1Ra incr. significant 0-7 days after onset, MCP-3 signif. upregulated throughout observation timecourse, and IP-10 increased and upregulated throughout (trending downwards over time).
- **The three cytokines together (IP-10, IL-1Ra, and MCP-3 AUC) served as the best predictors of disease deterioration and fatal outcome.**
- No significant differences between moderate/severe observed between groups in IL-2Ra, IL-6, IL-10, IL-18, CTACK, G-CSF, HGF, M-CSF, MIP-1a, MIG, and IFN γ at any timepoints.
- **Viral load (Lower Ct Value from qRT-PCR) was associated with upregulated IP-10 only (not IL-1Ra or MCP-3) and was highly correlated with decreased lung function: PaO₂/FaO₂ (arterial/atmospheric O₂) and Murray Score (lung injury).**
- **Antibodies against these cytokines (esp. anti-IP-10) may serve as a potential treatment for amelioration of COVID-19 (and associated ARDS).**

Lab results:

- **Decreased lymphocytes (%) in all patients – lymphopenia corr. w/ severe patients**
 - **Decreased CD4 and CD8 T cells** – no monocyte or eosino/basophil % measured
- **Increased neutrophils (%)**
- Increased BUN (mmol/L) – other kidney markers, liver markers, and LDH were not significantly different between groups and were not compared to healthy controls.

Clinical features (between moderate vs. severe patient groups):

- **Complications were associated with severity (ARDS, hepatic insufficiency, renal insufficiency).**
- Coexisting conditions between groups were not significantly different (chronic heart/lung/renal/liver disease, diabetes, or cancer) and patient time courses (onset to admission and onset to viral tx) also not significantly different – 4 days (2, 6) on average for admission and 4 (3,7) for antiviral.
- Increased corticosteroids and mechanical/ invasive mechanical ventilation in severe patients.
- Increased median age in severe group (Median (Range = 63.5 (42-74) vs. 51 (22-78)) and patients > 60 yrs had higher ratio of severe patients as compared patients 16-59 yrs.

- Higher incidence of fever in severe patients (91.2 vs. 68.4%), myalgia (57.7 vs. 48.1%), and chill (17.6% vs. 0%).
- No differences in cough, headache, nausea/vomiting, or diarrhea.

11.38.6 Significance

Outline of pathological time course (implicating innate immunity esp.) and identification key cytokines associated with disease severity and prognosis (+ comorbidities). Anti-IP-10 as a possible therapeutic intervention (ex: Eldelumab).

11.38.7 Credit

Review by Natalie Vaninov as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.39 Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019

Zhao Jr. et al. *medRxiv*. [[621](#)]

11.39.1 Keywords

- SARS-CoV-2 IgG
- seroconversion rate
- total Ab
- Ig
- IgM

11.39.2 Main Findings

This study examined antibody responses in the blood of COVID-19 patients during the early SARS CoV2 outbreak in China. Total 535 plasma samples were collected from 173 patients (51.4% female) and were tested for seroconversion rate using ELISA. Authors also compared the sensitivity of RNA and antibody tests over the course of the disease . The key findings are:

- Among 173 patients, the seroconversion rates for total antibody (Ab), IgM and IgG were 93.1% (161/173), 82.7% (143/173) and 64.7% (112/173), respectively.
- The seroconversion sequentially appeared for Ab, IgM and then IgG, with a median time of 11, 12 and 14 days, respectively. Overall, the seroconversion of Ab was significantly quicker than that of IgM ($p = 0.012$) and IgG ($p < 0.001$). Comparisons of seroconversion rates between critical and non-critical patients did not reveal any significant differences.
- RNA tests had higher sensitivity in early phase and within 7 days of disease onset than antibody assays (66.7% Vs 38.3% respectively).
- The sensitivity of the Ab assays was higher 8 days after disease onset, reached 90% at day 13 and 100% at later time points (15-39 days). In contrast, RNA was only detectable in 45.5% of samples at days 15-39.

- In patients with undetectable RNA in nasal samples collected during day 1-3, day 4-7, day 8-14 and day 15-39 since disease onset, 28.6% (2/7), 53.6% (15/28), 98.2% (56/57) and 100% (30/30) had detectable total Ab titers respectively. Combining RNA and antibody tests significantly raised the sensitivity for detecting COVID-19 patients in different stages of the disease ($p < 0.001$).
- There was a strong positive correlation between clinical severity and antibody titer 2-weeks after illness onset.
- Dynamic profiling of viral RNA and antibodies in representative COVID-19 patients ($n=9$) since onset of disease revealed that antibodies may not be sufficient to clear the virus. It should be noted that increases in of antibody titers were not always accompanied by RNA clearance.

11.39.3 Limitations

Because different types of ELISA assays were used for determining antibody concentrations at different time points after disease onset, sequential seroconversion of total Ab, IgM and IgG may not represent actual temporal differences but rather differences in the affinities of the assays used. Also, due to the lack of blood samples collected from patients in the later stage of illness, how long the antibodies could last remain unknown. For investigative dynamics of antibodies, more samples were required.

11.39.4 Significance

Total and IgG antibody titers could be used to understand the epidemiology of SARS CoV-2 infection and to assist in determining the level of humoral immune response in patients.

The findings provide strong clinical evidence for routine serological and RNA testing in the diagnosis and clinical management of COVID-19 patients. The understanding of antibody responses and their half-life during and after SARS CoV2 infection is important and warrants further investigations.

11.39.5 Credit

This review was undertaken by Zafar Mahmood and edited by K Alexandropoulos as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.40 Restoration of leukomonocyte counts is associated with viral clearance in COVID-19 hospitalized patients

Chen et al. *medRxiv* [[622](#)]

11.40.1 Keywords

- COVID-19
- T cell
- B cell
- NK cell
- IL-6
- pro-calcitonin
- cytokine storm

11.40.2 Main Findings

The authors collected data on 25 COVID-19 patients (n=11 men, n=14 women) using standard laboratory tests and flow cytometry. All patients were treated with antibiotics. Twenty-four of the 25 patients were also treated with anti-viral Umefinovir and 14 of the patients were treated with corticosteroids. 14 patients became negative for the virus after 8-14 days of treatment. The same treatment course was extended to 15-23 days for patients who were still positive for the virus at day 14.

The authors found a negative association between age and resolution of infection. Patients with hypertension, diabetes, malignancy or chronic liver disease were all unable to clear the virus at day 14, though not statistically significant.

Elevated procalcitonin and a trend for increased IL-6 were also found in peripheral blood prior to the treatment.

A trend for lower NK cell, T cell and B cell counts in patients was also reported. B cell, CD4 and CD8 T cell counts were only increased upon treatment in patients who cleared the virus. NK cell frequencies remained unchanged after treatment in all the patients.

11.40.3 Limitations

73% of the patients who remained positive for SARS-CoV2 after the 1st treatment, and 43% of all patients who cleared the virus were treated with corticosteroids. Corticosteroids have strong effects on the immune compartment in blood [623]. The authors should have accounted for corticosteroid treatment when considering changes in T, NK and B cell frequencies.

Assessing if IL-6 concentrations were back to baseline levels following treatment would have provided insights into the COVID-19 cytokine storm biology. Patients with higher baseline levels of IL-6 have been reported to have lower CD8 and CD4 T cell frequencies [619]. Correlating IL-6 with cell counts before and after treatment would thus have also been of interest. The report of the laboratory measures in table 2 is incomplete and should include the frequencies of patients with increased/decreased levels for each parameter.

Correction is needed for the 1st paragraph of the discussion as data does not support NK cell restoration upon treatment in patients who cleared the virus. NK cells remain unchanged after the 1st treatment course and only seem to increase in 2 out of 6 donors after the 2nd treatment course in those patients.

11.40.4 Significance

Previous reports suggest an association between disease severity and elevated IL-6 or pro-calcitonin concentrations in COVID-19 patients [615,624]. IL-6 receptor blockade is also being administered to patients enrolled in clinical trials (NCT04317092). This report thus contributes to highlight elevated concentrations of these analytes in COVID-19 patients. Mechanisms underlying the association between viral clearance and restoration of the T cell and B cell frequencies suggests viral-driven immune dysregulation, which needs to be investigated in further studies.

11.40.5 Credit

Review by Bérengère Salomé as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.41 Clinical findings in critically ill patients infected with SARS-CoV-2 in Guangdong Province, China: a multi-center, retrospective, observational study

Xu et al. *medRxiv*. [[625](#)]

11.41.1 Keywords

- clinical outcomes
- prognosis
- critically ill patients
- ICU
- lymphopenia
- LDH

11.41.2 Main Findings:

This work analyses laboratory and clinical data from 45 patients treated in the in ICU in a single province in China. Overall, 44% of the patients were intubated within 3 days of ICU admission with only 1 death.

Lymphopenia was noted in 91% of patient with an inverse correlation with LDH.

Lymphocyte levels are negatively correlated with Sequential Organ Failure Assessment (SOFA) score (clinical score, the higher the more critical state), LDH levels are positively correlated to SOFA score. Overall, older patients (>60yo), with high SOFA score, high LDH levels and low lymphocytes levels at ICU admission are at higher risk of intubation.

Of note, convalescent plasma was administered to 6 patients but due to limited sample size no conclusion can be made.

11.41.3 Limitations

While the study offers important insights into disease course and clinical lab correlates of outcome, the cohort is relatively small and is likely skewed towards a less-severe population compared to other ICU reports given the outcomes observed. Analysis of laboratory values and predictors of outcomes in larger cohorts will be important to make triage and treatment decisions. As with many retrospective analyses, pre-infection data is limited and thus it is not possible to understand whether lymphopenia was secondary to underlying comorbidities or infection.

Well-designed studies are necessary to evaluate the effect of convalescent plasma administration.

11.41.4 Significance

This clinical data enables the identification of at-risk patients and gives guidance for research for treatment options. Indeed, further work is needed to better understand the causes of the lymphopenia and its correlation with outcome.

11.41.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.42 Immune Multi-epitope vaccine design using an immunoinformatics approach for 2019 novel coronavirus in China (SARS-CoV-2)

[626]

11.42.1 Keywords

- Vaccine
- in silico
- B cell epitopes
- T cell epitopes

11.42.2 Main Findings

Using in silico bioinformatic tools, this study identified putative antigenic B-cell epitopes and HLA restricted T-cell epitopes from the spike, envelope and membrane proteins of SARS-CoV-2, based on the genome sequence available on the NCBI database. T cell epitopes were selected based on predicted affinity for the more common HLA-I alleles in the Chinese population. Subsequently, the authors designed vaccine peptides by bridging selected B-cell epitopes and adjacent T-cell epitopes. Vaccine peptides containing only T-cell epitopes were also generated.

From 61 predicted B-cell epitopes, only 19 were exposed on the surface of the virion and had a high antigenicity score. A total of 499 T-cell epitopes were predicted. Based on the 19 B-cell epitopes and their 121 adjacent T-cell epitopes, 17 candidate vaccine peptides were designed. Additionally, another 102 vaccine peptides containing T-cell epitopes only were generated. Based on the epitope counts and HLA score, 13 of those were selected. Thus, a total of 30 peptide vaccine candidates were designed.

11.42.3 Limitations

While this study provides candidates for the development of vaccines against SARS-CoV-2, in vitro and in vivo trials are required to validate the immunogenicity of the selected B and T cell epitopes. This could be done using serum and cells from CoV-2-exposed individuals, and in preclinical studies. The implication of this study for the current epidemic are thus limited. Nevertheless, further research on this field is greatly needed.

11.42.4 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.43 Clinical Features of Patients Infected with the 2019 Novel Coronavirus (COVID-19) in Shanghai, China

Cao et al. *medRxiv* [627]

11.43.1 Keywords

- Disease severity
- clinical features
- laboratory abnormalities

11.43.2 Main Findings

This single-center cohort study analyzes the clinical and laboratory features of 198 patients with confirmed COVID-19 infection in Shanghai, China and correlated these parameters with clinical disease severity, including subsequent intensive care unit (ICU) admission. 19 cases (9.5%) required ICU admission after developing respiratory failure or organ dysfunction. Age, male sex, underlying cardiovascular disease, and high symptom severity (high fever, dyspnea) were all significantly correlated with ICU admission. Additionally, ICU admission was more common in patients who presented with lymphopenia and elevated neutrophil counts, among other laboratory abnormalities. Flow cytometric analysis revealed that patients admitted to the ICU had significantly reduced circulating CD3+ T cell, CD4+ T cell, CD8+ T cell, and CD45+ leukocyte populations compared to the cohort of patients not requiring ICU admission.

11.43.3 Limitations

The limitations of this study include the relatively small sample size and lack of longitudinal testing. The authors also did not assess whether respiratory comorbidity – such as asthma or chronic obstructive lung disease – in addition to immunosuppression affected ICU admission likelihood.

11.43.4 Significance

COVID-19 has already sickened thousands across the globe, though the severity of these infections is markedly diverse, ranging from mild symptoms to respiratory failure requiring maximal intervention. Understanding what clinical, laboratory, and immunologic factors predict the clinical course of COVID-19 infection permits frontline providers to distribute limited medical resources more effectively.

11.43.5 Credit

Review by Andrew Charap as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine at Mount Sinai.

11.44 Serological detection of 2019-nCoV respond to the epidemic: A useful complement to nucleic acid testing

Zhang et al. *medRxiv*. [[628](#)]

11.44.1 Keywords

- Immunoassay
- serum IgM and IgG
- specific antibodies

11.44.2 Main Finding

This study showed that both anti-2019-nCoV IgM and IgG were detected by automated chemiluminescent immunoassay in the patients who had been already confirmed as positive by nucleic acid detection, while single positivity of IgM or IgG were detected in a very few cases in the other population including 225 non-COVID-19 cases. In addition to the increase of anti-2019-nCoV IgM 7-12 days after morbidity, the increase of IgG was detected in three patients with COVID-19 within a very short of time (0-1 day).

11.44.3 Limitations

The limitation of this study is only 3 confirmed COVID-19 cases were included, so that the relationship between anti-2019-nCov antibodies and disease progression might not be clearly defined. Another limitation is that they did not show the course of 2019-nCov specific antibodies in the cases with positive for COVID-19 but without clinical symptoms.

11.44.4 Significance

The detection of anti-2019-nCov antibodies can be an alternative method to diagnose and treat COVID-19 more comprehensively by distinguish non COVID-19 patients. It may be helpful to understand the course of individual cases with COVID-19 to predict the prognosis if more cases will be evaluated.

11.44.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.45 Human Kidney is a Target for Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

[\[629\]](#)

11.45.1 Keywords

- Kidney/Renal Failure
- Macrophage Infiltration
- Complement Activation

11.45.2 Main Finding

Analyzing the eGFR (effective glomerular flow rate) of 85 Covid-19 patients and characterizing tissue damage and viral presence in post-mortem kidney samples from 6 Covid-19 patients, the authors conclude that significant damage occurs to the kidney, following Covid-19 infection. This is in contrast to the SARS infection from the 2003 outbreak. They determine this damage to be more prevalent in patients older than 60 years old, as determined by analysis of eGFR. H&E and IHC analysis in 6 Covid-19 patients revealed that damage was in the tubules, not the glomeruli of the kidneys and suggested that macrophage accumulation and C5b-9 deposition are key to this process.

11.45.3 Limitations

Severe limitations include that the H&E and IHC samples were performed on post-mortem samples of unknown age, thus we cannot assess how/if age correlates with kidney damage, upon Covid-19 infection. Additionally, eGFR was the only *in-vivo* measurement. Blood urea nitrogen and proteinuria are amongst other measurements that could have been obtained from patient records. An immune panel of the blood was not performed to assess immune system activation. Additionally, patients are only from one hospital.

11.45.4 Significance

This report makes clear that kidney damage is prevalent in Covid-19 patients and should be accounted for.

11.45.5 Credit

Review by Dan Fu Ruan, Evan Cody and Venu Pothula as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine at Mount Sinai.

11.46 COVID-19 early warning score: a multi-parameter screening tool to identify highly suspected patients

Song et al. *medRxiv*. [[630](#)]

11.46.1 Keywords

- retrospective
- electronic health records
- blood counts
- diagnostic
- prognostic
- modeling

11.46.2 Main Findings

The aim of this study was to identify diagnostic or prognostic criteria which could identify patients with COVID-19 and predict patients who would go on to develop severe respiratory disease. The authors use EMR data from individuals taking a COVID-19 test at Zhejiang hospital, China in late January/Early February. A large number of clinical parameters were different between individuals with COVID-19 and also between 'severe' and 'non-severe' infections and the authors combine these into a multivariate linear model to derive a weighted score, presumably intended for clinical use.

11.46.3 Limitations

Unfortunately, the paper is lacking a lot of crucial information, making it impossible to determine the importance or relevance of the findings. Most importantly, the timings of the clinical measurements are not described relative to the disease course, so it is unclear if the differences between 'severe' and 'non-severe' infections are occurring before progression to severe disease (which would make them useful prognostic markers), or after (which would not).

11.46.4 Significance

This paper is one of many retrospective studies coming from hospitals in China studying individuals with COVID-19. Because of the sparse description of the study design, this paper offers little new information. However, studies like this could be very valuable and we would strongly encourage the authors to revise this manuscript to include more information about the timeline of clinical measurements in relation to disease onset and more details of patient outcomes.

11.46.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.47 LY6E impairs coronavirus fusion and confers immune control of viral disease

11.47.1 Keywords

- interferon-stimulated genes
- antiviral interferons
- human coronaviruses (CoV)
- murine hepatitis virus (MHV)

11.47.2 Main Findings

Screening a cDNA library of >350 human interferon-stimulated genes for antiviral activity against endemic human coronavirus HCoV-229E (associated with the common cold), Pfaender S & Mar K *et al.* identify lymphocyte antigen 6 complex, locus E (Ly6E) as an inhibitor of cellular infection of Huh7 cells, a human hepatoma cell line susceptible to HCoV-229E and other coronaviruses. In a series of consecutive *in vitro* experiments including both stable Ly6E overexpression and CRISPR-Cas9-mediated knockout the authors further demonstrate that Ly6E reduces cellular infection by various other coronaviruses including human SARS-CoV and SARS-CoV-2 as well as murine CoV mouse hepatitis virus (MHV). Their experiments suggest that this effect is dependent on Ly6E inhibition of CoV strain-specific spike protein-mediated membrane fusion required for viral cell entry.

To address the function of Ly6E *in vivo*, hematopoietic stem cell-specific Ly6E knock-out mice were generated by breeding Ly6E^{fl/fl} mice (referred to as functional wild-type mice) with transgenic *Vav-iCre* mice (offspring referred to as Ly6E HSC ko mice); wild-type and Ly6E HSC ko mice of both sexes were infected intraperitoneally with varying doses of the natural murine coronavirus MHV, generally causing a wide range of diseases in mice including hepatitis, enteritis and encephalomyelitis. Briefly, compared to wild-type controls, mice lacking hematopoietic cell-expressed Ly6E were found to present with a more severe disease phenotype as based on serum ALT levels (prognostic of liver damage), liver histopathology, and viral titers in the spleen. Moreover, bulk RNAseq analysis of infected liver and spleen tissues indicated changes in gene expression pathways related to tissue damage and antiviral immune responses as well as a reduction of genes associated with type I IFN response and inflammation. Finally, the authors report substantial differences in the numbers of hepatic and splenic APC subsets between wild-type and knockout mice following MHV infection and show that Ly6E-deficient B cells and to a lesser extent also DCs are particularly susceptible to MHV infection *in vitro*.

11.47.3 Limitations

Experiments and data in this study are presented in an overall logical and coherent fashion; however, some observations and the conclusions drawn are problematic and should be further addressed & discussed by the authors. Methodological & formal limitations include relatively low replicate numbers as well as missing technical replicates for some *in vitro* experiments (*cf.* Fig. legend 1; Fig. legend 2e); the omission of “outliers” in Fig. legend 2 without an apparent rationale as to why this approach was chosen; the lack of detection of actual Ly6E protein levels in Ly6E HSC ko or wild-type mice; and most importantly, missing information on RNAseq data collection & analysis in the method section and throughout the paper. A more relevant concern though is that the interpretation of the experimental data presented and the language used tend to overrate and at times overgeneralize findings: for example, while the authors demonstrate statistically significant, Ly6E-mediated reduction of coronavirus titers in stable cells lines *in vitro*, it remains unclear whether a viral titer reduction by one log decade would be of actual biological relevance in face of high viral titers *in vivo*. After high-dose intraperitoneal MHV infection *in vivo*, early viral titers in Ly6E HSC knockout vs. wt mice only showed an elevation in the spleen (~1.5 log decades) but not liver of the ko mice (other tissue not evaluated), and while ko mice presented with only modestly increased liver pathology, both male and

female ko mice exhibited significantly higher mortality. Thus, the manuscript title statement that “Ly6E ... confers immune control of viral disease” is supported by only limited *in vivo* data, and gain-of-function experiments (eg. Ly6E overexpression) were not performed. Of additional note here, tissue tropism and virulence differ greatly among various MHV strains and isolates whereas dose, route of infection, age, genetic background and sex of the mice used may additionally affect disease outcome and phenotype (*cf.* Taguchi F & Hirai-Yuki A, <https://doi.org/10.3389/fmicb.2012.00068>; Kanolkhar A et al, <https://jvi.asm.org/content/83/18/9258>). Observations attributed to hematopoietic stem cell-specific Ly6E deletion could therefore be influenced by the different genetic backgrounds of floxed and cre mice used, and although it appears that littermates wt and ko littermates were used in the experiments, the potentially decisive impact of strain differences should at least have been discussed. Along these lines, it should also be taken into account that the majority of human coronaviruses cause respiratory symptoms, which follow a different clinical course engaging other primary cellular mediators than the hepatotropic murine MHV disease studied here. It therefore remains highly speculative how the findings reported in this study will translate to human disease and it would therefore be important to test other routes of MHV infection and doses that have been described to produce a more comparable phenotype to human coronavirus disease (*cf.* Kanolkhar A et al, <https://jvi.asm.org/content/83/18/9258>). Another important shortcoming of this study is the lack of any information on functional deficits or changes in Ly6E-deficient immune cells and how this might relate to the phenotype observed. Overall, the *in vitro* experiments are more convincing than the *in vivo* studies which appear somewhat limited.

11.47.4 Significance

Despite some shortcomings, the experiments performed in this study suggest a novel and somewhat unexpected role of Ly6E in the protection against coronaviruses across species. These findings are of relevance and should be further explored in ongoing research on potential coronavirus therapies. Yet an important caveat pertains to the authors’ suggestion that “therapeutic mimicking of Ly6E action” may constitute a first line of defense against novel coronaviruses since their own prior work demonstrated that Ly6E can enhance rather than curtail infection with influenza A and other viruses.

11.47.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.48 A preliminary study on serological assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 238 admitted hospital patients

Liu et al. *medRxiv.* [[632](#)]

11.48.1 Keywords

- diagnosis
- serological assay
- ELISA
- RT-PCR

11.48.2 Main Findings

While RT-PCR is being used currently to routinely diagnose infection with SARS-CoV-2, there are significant limitations to the use of a nucleic acid test that lead to a high false-negative rate. This article describes ELISAs that can measure IgM and IgG antibodies against the N protein of SARS-CoV-2

to test samples from 238 patients (153 positive by RT-PCR and 85 negative by RT-PCR) at different times after symptom onset. The positivity rate of the IgM and/or IgG ELISAs was greater than that of the RT-PCR (81.5% compared to 64.3%) with similar positive rates in the confirmed and suspected cases (83% and 78.8%, respectively), suggesting that many of the suspected but RT-PCR-negative cases were also infected. The authors also found that the ELISAs have higher positive rates later after symptom onset while RT-PCR is more effective as a diagnostic test early during the infection.

11.48.3 Limitations

I cannot identify any limitations to this study.

11.48.4 Significance

The authors make a strong case for using a combination of ELISA and RT-PCR for diagnosis of infection with SARS-CoV-2, especially considering the dynamics of positivity rates of RT-PCR and ELISA. Fewer false-negative diagnoses would improve infection control and patient management.

11.48.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.49 Monoclonal antibodies for the S2 subunit of spike of SARS-CoV cross-react with the newly-emerged SARS-CoV-2

[\[633\]](#)

11.49.1 Keywords

- Coronavirus Disease 2019 (COVID-19)
- SARS-CoV-2
- Spike protein
- Cross- reactive antibodies

11.49.2 Main Findings

Whole genome sequencing-based comparisons of the 2003 Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the 2019 SARS-CoV-2 revealed conserved receptor binding domain (RBD) and host cell receptor, angiotensin-converting enzyme 2 (ACE2). In line with this, the authors tested cross-reactivity of murine monoclonal antibodies (mAbs) previously generated against the SARS-CoV spike (S) glycoprotein involved in viral entry. One of the screened mAb, 1A9, was able to bind and cross-neutralize multiple strains of SARS-CoV, as well as, detect the S protein in SARS-CoV-2-infected cells. mAb 1A9 was generated using an immunogenic fragment in the S2 subunit of SARS-CoV and binds through a novel epitope within the S2 subunit at amino acids 1111-1130. It is important to note that CD8+ T lymphocyte epitopes overlap with these residues, suggesting that S2 subunit could be involved in inducing both, humoral and cell-mediated immunity.

11.49.3 Limitations

The authors used previously generated mouse mAbs against the S protein in SARS-CoV expressed in mammalian cell line. Future experimental validation using COVID-19 patient samples is needed to validate these findings. In addition, the results of these studies are predominantly based on in vitro

experiments and so, evaluating the effects of the mAb 1A9 in an animal model infected with this virus will help us better understand the host immune responses in COVID-19 and potential therapeutic vaccines.

11.49.4 Significance

This study identified mAbs that recognize the new coronavirus, SARS-Cov-2. These cross-reactive mAbs will help in developing diagnostic assays for COVID-19.

11.49.5 Credit

This review was undertaken by Tamar Plitt and Katherine Lindblad as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.50 Mortality of COVID-19 is Associated with Cellular Immune Function Compared to Immune Function in Chinese Han Population

Zeng et al. *medRxiv*. [[634](#)]

11.50.1 Keywords

- WBC
- peripheral blood
- CD4
- CD8 T cells

11.50.2 Main Findings

Retrospective study of the clinical characteristics of 752 patients infected with COVID-19 at Chinese PLA General Hospital, Peking Union Medical College Hospital, and affiliated hospitals at Shanghai University of medicine & Health Sciences. This study is the first one that compares PB from healthy controls from the same regions in Shanghai and Beijing, and infected COVID-19 patients to standardize a reference range of WBCs of people at high risk.

11.50.3 Limitations

Lower levels of leukocyte counts -B cells, CD4 and CD8 T cells- correlated with mortality (WBCs are significantly lower in severe or critical UCI patients vs mild ones). Based on 14,117 normal controls in Chinese Han population (ranging in age from 18-86) it is recommended that reference ranges of people at high risk of COVID-19 infection are CD3+ lymphocytes below 900 cells/mm³, CD4+ lymphocytes below 500 cells/mm³, and CD8+ lymphocytes below 300 cells/mm³. Importantly, this study also reported that the levels of D-dimer, C-reactive protein and IL-6 were elevated in COVID-19 pts., indicating clot formation, severe inflammation and cytokine storm.

11.50.4 Significance

This study sets a threshold to identify patients at risk by analyzing their levels of leukocytes, which is an easy and fast approach to stratify individuals that require hospitalization. Although the study is limited (only counts of WBC are analyzed and not its profile) the data is solid and statistically robust to correlate levels of lymphopenia with mortality.

11.50.5 Credit

11.51 Retrospective Analysis of Clinical Features in 101 Death Cases with COVID-19

Chen et al. *medRxiv*. [[635](#)]

11.51.1 Keywords

- death biomarkers
- cardiac damage
- Troponin
- Blood type
- respiratory failure
- hypertension

11.51.2 Main Findings

This is a retrospective study involving 101 death cases with COVID-19 in Wuhan Jinyintan Hospital. The aim was to describe clinical, epidemiological and laboratory features of fatal cases in order to identify the possible primary mortality causes related to COVID-19.

Among 101 death cases, 56.44% were confirmed by RT-PCR and 43.6% by clinical diagnostics. Males dominated the number of deaths and the average age was 65.46 years. All patients died of respiratory failure and multiple organs failure, except one (acute coronary syndrome). The predominant comorbidities were hypertension (42.57%) and diabetes (22.77%). 25.74% of the patients presented more than two underlying diseases. 82% of patients presented myocardial enzymes abnormalities at admission and further increase in myocardial damage indicators with disease progression: patients with elevated Troponin I progressed faster to death. Alterations in coagulation were also detected. Indicators of liver and kidney damage increased 48 hours before death. The authors studied the deceased patients' blood type and presented the following results: type A (44.44%), type B (29.29%), type AB (8.08%) and type O (18.19%), which is inconsistent with the distribution in Han population in Wuhan.

Clinical analysis showed that the most common symptom was fever (91.9%), followed by cough and dyspnea. The medium time from onset of symptoms to acute respiratory distress syndrome (ARDS) development was 12 days. Unlike SARS, only 2 patients with COVID-19 had diarrhea. 98% presented abnormal lung imaging at admission and most had double-lung abnormalities. Related to the laboratorial findings some inflammatory indicators gradually increased during the disease progression, such as IL-6 secretion in the circulation, procalcitonin (PCT) and C-reactive protein (CRP), while platelets numbers decreased. The authors also reported an initial lymphopenia that was followed by an increase in the lymphocytes numbers. Neutrophil count increased with disease progression.

The patients received different treatments such as antiviral drugs (60.40%), glucocorticoids, thymosin and immunoglobulins. All patients received antibiotic treatment and some received antifungal drugs. All patients received oxygen therapy (invasive or non-invasive ones).

11.51.3 Limitations

This study involves just fatal patients, lacking comparisons with other groups of patients e.g. patients that recovered from COVID-19. The authors didn't discuss the different approaches used for treatments and how these may affect the several parameters measured. The possible relationship between the increase of inflammatory indicators and morbidities of COVID-19 are not discussed.

11.51.4 Significance

This study has the largest cohort of fatal cases reported so far. The authors show that COVID-19 causes fatal respiratory distress syndrome and multiple organ failure. This study highlights prevalent myocardial damage and indicates that cardiac function of COVID-19 patients should be carefully monitored. The data suggest that Troponin I should be further investigated as an early indicator of patients with high risk of accelerated health deterioration. Secondary bacterial and fungal infections were frequent in critically ill patients and these need to be carefully monitored in severe COVID-19 patients. Differences in blood type distribution were observed, suggesting that type A is detrimental while type O is protective – but further studies are needed to confirm these findings and elucidate if blood type influences infection or disease severity. Several inflammatory indicators (neutrophils, PCT, CRP and IL-6, D-dimer) increased according to disease severity and should be assessed as biomarkers and to better understand the biology of progression to severe disease.

11.51.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.52 Relationship between the ABO Blood Group and the COVID-19 Susceptibility

Zhao et al. *medRxiv*. [[636](#)]

11.52.1 Keywords

- ABO blood group
- COVID-19 susceptibility

11.52.2 Main Findings

These authors compared the ABO blood group of 2,173 patients with RT-PCR-confirmed COVID-19 from hospitals in Wuhan and Shenzhen with the ABO blood group distribution in unaffected people in the same cities from previous studies (2015 and 2010 for Wuhan and Shenzhen, respectively). They found that people with blood group A are statistically over-represented in the number of those infected and who succumb to death while those with blood group O are statistically underrepresented with no influence of age or sex.

11.52.3 Limitations

This study compares patients with COVID-19 to the general population but relies on data published 5 and 10 years ago for the control. The mechanisms that the authors propose may underlie the differences they observed require further study.

11.52.4 Significance

Risk stratification based on blood group may be beneficial for patients and also healthcare workers in infection control. Additionally, investigating the mechanism behind these findings could lead to better developing prophylactic and therapeutic targets for COVID-19.

11.52.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.53 The inhaled corticosteroid ciclesonide blocks coronavirus RNA replication by targeting viral NSP15

Matsuyama et al. *bioRxiv* [[637](#)]

11.53.1 Keywords

- Corticosteroids
- ciclesonide
- mometasone
- NSP15
- MERS-CoV

11.53.2 Main Findings

This study reconsiders the use of inhaled corticosteroids in the treatment of pneumonia by coronavirus. Corticosteroids were associated with increased mortality for SARS in 2003 and for MERS in 2013, probably due to that fact that systemic corticosteroids suppress the innate immune system, resulting in increased viral replication. However, some steroid compounds might block coronavirus replication. The authors screened steroids from a chemical library and assessed the viral growth suppression and drug cytotoxicity. Ciclesonide demonstrated low cytotoxicity and potent suppression of MERS-CoV viral growth. The commonly used systemic steroids cortisone, prednisolone and dexamethasone did not suppress viral growth, nor did the commonly used inhaled steroid fluticasone. To identify the drug target of virus replication, the authors conducted 11 consecutive MERS-CoV passages in the presence of ciclesonide or mometasone, and they could generate a mutant virus that developed resistance to ciclesonide, but not to mometasone. Afterwards, they performed next-generation sequencing and identified an amino acid substitution in nonstructural protein 15 (NSP15) as the predicted mechanism for viral resistance to ciclesonide. The authors were able to successfully generate a recombinant virus carrying that amino acid substitution, which overcome the antiviral effect of ciclesonide, suggesting that ciclesonide interacts with NSP15. The mutant virus was inhibited by mometasone, suggesting that the antiviral target of mometasone is different from that of ciclesonide. Lastly, the effects of ciclesonide and mometasone on suppressing the replication of SARS-CoV-2 were evaluated. Both compounds were found to suppress viral replication with a similar efficacy to lopinavir.

11.53.3 Limitations

Most of the experiments, including the identification of the mutation in NSP15 were conducted with MERS-CoV. This is not the closest related virus to SARS-CoV-2, as that would be SARS-CoV. Thus, to repeat the initial experiments with SARS-CoV, or preferably SARS-CoV-2, is essential. The manuscript should address this and, therefore, it will require considerable editing for organization and clarity. Also, in terms of cell immunogenic epitopes, while SARS-CoV-2 spike protein contains several predicted B and T cell immunogenic epitopes that are shared with other coronaviruses, some studies

have shown critical differences between MERS-CoV, SARS-CoV and SARS-CoV-2. A main criticism is that the authors only used VeroE6/TMPRSS2 cells to gauge the direct cytotoxic effects of viral replication. To evaluate this in other cell lines, including human airway epithelial cells, is crucial, as the infectivity of coronavirus strains greatly varies in different cell lines,

11.53.4 Significance

Nevertheless, these findings encourage evaluating ciclesonide and mometasone as better options for patients with COVID-19 in need of inhaled steroids, especially as an alternative to other corticosteroids that have been shown to increase viral replication in vitro. This should be evaluated in future clinical studies.

11.53.5 Credit

This review was undertaken by Alvaro Moreira, MD as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.54 A human monoclonal antibody blocking SARS-CoV-2 infection **

Wang et al. *bioRxiv*. [[495](#)]

11.54.1 Keywords

- Monoclonal antibodies
- SARS-CoV2
- cross-neutralization
- potential treatment
- spike receptor

11.54.2 Main Findings

The authors reported a human monoclonal antibody that neutralizes SARS-CoV-2 and SARS-Cov which belong to same family of corona viruses. For identifying mAbs, supernatants of a collection of 51 hybridomas raised against the spike protein of SARS-CoV (SARS-S) were screened by ELISA for cross-reactivity against the spike protein of SARS-CoN2 (SARS2-S). Hybridomas were derived from immunized transgenic H2L2 mice (chimeric for fully human VH-VL and rat constant region). Four SARS-S hybridomas displayed cross-reactivity with SARS2-S, one of which (47D11) exhibited cross-neutralizing activity for SARS-S and SARS2-S pseudotyped VSV infection. A recombinant, fully human IgG1 isotype antibody was generated and used for further characterization.

The humanized 47D11 antibody inhibited infection of VeroE6 cells with SARS-CoV and SARS-CoV-2 with IC50 values of 0.19 and 0.57 µg/ml respectively. 47D11 mAb bound a conserved epitope on the spike receptor binding domain (RBD) explaining its ability to cross-neutralize SARS-CoV and SARS-CoV-2. 47D11 was shown to target the S1B RBD of SARS-S and SARS2-S with similar affinities. Interestingly, binding of 47D11 to SARS-S1B and SARS2-S1B did not interfere with S1B binding to ACE2 receptor-expressing cells assayed by flow cytometry.

11.54.3 Limitations

These results show that the human 47D11 antibody neutralizes SARS-CoV and SARS-Cov2 infectivity via an as yet unknown mechanism that is different from receptor binding interference. Alternative mechanisms were proposed but these as yet remain to be tested in the context of SARS-CoV2. From a

therapeutic standpoint and in the absence of in vivo data, it is unclear whether the 47D11 ab can alter the course of infection in an infected host through virus clearance or protect an uninfected host that is exposed to the virus. There is a precedent for the latter possibility as it relates to SARS-CoV that was cited by the authors and could turn out to be true for SARS-CoV2.

11.54.4 Significance

This study enabled the identification of novel neutralizing antibody against COV-that could potentially be used as first line of treatment in the near future to reduce the viral load and adverse effects in infected patients. In addition, neutralizing antibodies such as 47D11 represent promising reagents for developing antigen-antibody-based detection test kits and assays.

11.54.5 Credit

This review was edited by K. Alexandropoulos as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

Heat inactivation of serum interferes with the immunoanalysis of antibodies to SARS-CoV-2

Heat inactivation, immunochromatography, diagnosis, serum antibodies, IgM, IgG

Summary

The use of heat inactivation to neutralize pathogens in serum samples collected from suspected COVID-19 patients reduces the sensitivity of a fluorescent immunochromatographic assay to detect anti-SARS-CoV-2 IgM and IgG.

Major findings

Coronaviruses can be killed by heat inactivation, and this is an important safety precaution in laboratory manipulation of clinical samples. However, the effect of this step on downstream SARS-CoV-2-specific serum antibody assays has not been examined. The authors tested the effect of heat inactivation (56 deg C for 30 minutes) versus no heat inactivation on a fluorescence immunochromatography assay. Heat inactivation reduced all IgM measurements by an average of 54% and most IgG measurements (22/36 samples, average reduction of 50%), consistent with the lower thermal stability of IgM than that of IgG. Heat inactivation caused a subset of IgM but not IgG readings to fall below a specified positivity threshold.

Limitations

Limitations included the use of only one type of assay for testing heat inactivated vs non-inactivated sera, and the use of the same baseline for heat inactivated and non-inactivated sera. The results indicate that heat inactivation affects the quantification of SARS-CoV-2-antibody response, specially IgM, but still allows to distinguish positive specific IgG. Therefore, the effect of heat inactivation should be studied when designing assays that quantitatively associate immunoglobulin levels (especially IgM) to immune state.

Review by Andrew M. Leader as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn school of medicine, Mount Sinai.

11.55 Immune phenotyping based on neutrophil-to-lymphocyte ratio and IgG predicts disease severity and outcome for patients with COVID-19

11.55.1 Keywords

- Biomarkers
- cytokines
- IgG
- immune cells

11.55.2 Main Findings

In a cohort of 222 patients, anti-SARS-CoV-2 IgM and IgG levels were analyzed during acute and convalescent phases (up to day 35) and correlated to the diseases' severity. The same was done with neutrophil-to-lymphocyte ratio. High IgG levels and high neutrophil-to-lymphocyte ratio in convalescence were both independently associated to the severity of the disease. The simultaneous occurrence of both of these laboratory findings correlated even stronger to the diseases' severity.

Severe cases with high neutrophil-to-lymphocyte ratios had clearly higher levels of IL-6. The authors propose that a robust IgG response leads to immune-mediated tissue damage, thus explaining the worse outcome in patients with overexuberant antibody response.

11.55.3 Limitations

A main criticism is that the criteria for stratifying patients in severe vs. non-severe are not described. The only reference related to this is the difference between the percentage of patients who needed mechanical ventilation, which was greater in patients with both high IgG levels and high neutrophil-to-lymphocyte ratio. No patient with both low IgG levels and low neutrophil-to-lymphocyte ratio was treated with mechanical ventilation.

The proposed correlation of severity with IL-2 and IL-10 levels is not very strong.

Furthermore, although mostly ignored in the paper's discussion, one of the most interesting findings is that an early increase in anti-SARS-CoV-2 IgM levels also seems to correlate with severe disease. However, as only median values are shown for antibody kinetics curves, the extent of variation in acute phase cannot be assessed.

11.55.4 Significance

Anti-SARS-CoV-2 IgG levels and with neutrophil-to-lymphocyte ratio predict severity of COVID-19 independently of each other. An additive predictive value of both variables is noticeable. Importantly, an early-on increase in anti-SARS-CoV-2 IgM levels also seem to predict outcome.

11.55.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.56 Reinfection could not occur in SARS-2 CoV-2 infected rhesus macaques

11.56.1 Keywords

- SARS-CoV-2
- viral load
- reinfection
- relapse
- non-human primate model

11.56.2 Main Findings

This study addresses the issue of acquired immunity after a primary COVID-19 infection in rhesus monkeys. Four Chinese rhesus macaques were intratracheally infected with SARS-CoV-2 and two out of the four were re-infected at 28 days post initial infection (dpi) with the same viral dose after confirming the recovery by the absence of clinical symptoms, radiological abnormalities and viral detection (2 negative RT-PCR tests). While the initial infection led the viral loads in nasal and pharyngeal swabs that reach approximately $6.5 \log_{10}$ RNA copies/ml at 3 dpi in all four monkeys, viral loads in the swabs tested negative after reinfection in the two reinfected monkeys. In addition, the necropsies from a monkey (M1) at 7 days after primary infection, and another monkey (M3) at 5 days post reinfection, revealed the histopathological damages and viral replication in the examined tissues from M1, while no viral replication as well as no histological damages were detected in the tissues from M3. Furthermore, sera from three monkeys at 21 and 28 dpi exhibited neutralizing activity against SARS-CoV-2 in vitro, suggesting the production of protective neutralizing antibodies in these monkeys. Overall, this study indicates that primary infection with SARS-CoV-2 may protect from subsequent exposure to the same virus.

11.56.3 Limitations

In human, virus has been detected by nasopharyngeal swabs until 9 to 15 days after the onset of symptoms. In the infected monkeys in this study, virus were detected from day 1 after the infection, declining to undetectable level by day 15 post infection. It may suggest that there is a faster viral clearance mechanism in monkeys, therefore the conclusions of reinfection protection for humans need to be carefully considered. In addition, only two monkeys were re-infected in this study and the clinical signs of these monkeys were not similar: M3 did not show weight loss and M4 showed relatively higher fever on the day of infection and the day of re-challenge.

11.56.4 Significance

This study showed clear viral clearance and no indications of relapse or viremia after a secondary infection with SARS-CoV-2 in a Chinese rhesus macaque model. These results support the idea that patients with full recovery (two negative RT-PCR results) may also be protected from secondary SARS-CoV-2 infection. Recovered patients may be able to reintegrate to normal public life and provide protective serum perhaps even if having had a mild infection. The results are also encouraging for successful vaccine development against SARS-CoV-2.

11.56.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.57 A highly conserved cryptic epitope in the receptor-binding domains of SARS-CoV-2 and SARS-CoV

11.57.1 Keywords

- neutralizing antibody
- cross-reactivity

11.57.2 Main Findings

Given the sequence similarity of the surface spike glycoprotein (S) of SARS-CoV-2 and SARS-CoV, Yuan et al. (2020) propose that neutralizing antibodies isolated from convalescent SARS-CoV patients may offer insight into cross-reactive antibodies targeting SARS-CoV-2. In particular, they find that the receptor-binding domain (RBD) of SARS-CoV-2 S protein shares 86% sequence similarity with the RBD of SARS-CoV S protein that binds to the CR3022 neutralizing antibody. CR3022 also displays increased affinity for the “up” conformation of the SARS-CoV-2 S protein compared to the “down” conformation as it does for the SARS-CoV S protein. Therefore, the authors propose that this cross-reactive antibody may confer some degree of protection *in vivo* even if it fails to neutralize *in vitro*.

11.57.3 Limitations

Although the authors offer a logical rationale for identifying cross-reactive neutralizing antibodies derived from SARS-CoV, their study using only CR3022 failed to demonstrate whether this approach will be successful. After all, CR3022 failed to neutralize *in vitro* despite the binding affinity to a similar epitope on SARS-CoV-2. They would benefit from testing more candidates and using an *in vivo* model to demonstrate their claim that protection may be possible in the absence neutralization if combinations are used *in vivo*.

11.57.4 Significance

The ability to make use of previously characterized neutralizing antibodies for conserved epitopes can expedite drug design and treatment options.

11.57.5 Credit

This review was undertaken by Dan Fu Ruan, Evan Cody and Venu Pothula as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.58 Highly accurate and sensitive diagnostic detection of SARS-CoV-2 by digital PCR

Dong et al. *medRxiv* [[222](#)]

11.58.1 Keywords

- Diagnosis
- digital PCR

11.58.2 Main Findings

The authors present a digital PCR (dPCR) diagnostic test for SARS-CoV-2 infection. In 103 individuals that were confirmed in a follow-up to be infected, the standard qPCR test had a positivity rate of 28.2% while the dPCR test detected 87.4% of the infections by detecting an additional 61 positive cases. The authors also tested samples from close contacts (early in infection stage) and convalescing

individuals (late in infection stage) and were able to detect SARS-CoV-2 nucleic acid in many more samples using dPCR compared to qPCR.

11.58.3 Limitations

I did not detect limitations.

11.58.4 Significance

The authors make a strong case for the need for a highly sensitive and accurate confirmatory method for diagnosing COVID-19 during this outbreak and present a potential addition to the diagnostic arsenal. They propose a dPCR test that they present has a dramatically lower false negative rate than the standard RT-qPCR tests and can be especially beneficial in people with low viral load, whether they are in the earlier or later stages of infection.

11.58.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.59 SARS-CoV-2 invades host cells via a novel route: CD147-spike protein

Wang et al. *bioRxiv* [[641](#)]

11.59.1 Keywords

- spike protein
- viral entry
- CD147
- SARS-CoV-2

11.59.2 Main Findings

The authors propose a novel mechanism of SARS-CoV-2 viral entry through the interaction of the viral spike protein (SP) and the immunoglobulin superfamily protein CD147 (also known as Basigin). Using an in-house developed humanized antibody against CD147 (maplazumab), they show that blocking CD147 decreases viral replication in Vero E6 cells. Using surface plasmon resonance (SPR), ELISA, and Co-IP assays, they show that the spike protein of SARS-CoV-2 directly interacts with CD147. Lastly, they utilize immune-electron microscopy to show spike protein and CD147 localize to viral inclusion bodies of Vero E6 cells.

11.59.3 Limitations

The authors claim that an anti-CD147 antibody (Meplazumab) inhibits SARS-CoV-2 replication by testing cell growth and viral load in cells infected with SARS-CoV-2, however there are key pieces of this experiment that are missing. First, the authors fail to use a non-specific antibody control. Second, the authors claim that viral replication is inhibited, and that they test this by qPCR, however this data is **not shown**. To further prove specificity, the authors should introduce CD147 to non-susceptible cells and show that they become permissive.

The authors claim that there is a direct interaction between CD147 and SP through SPR, ELISA, and Co-IP, and this data seems generally convincing. The electron microscopy provides further correlative

evidence that SARS-CoV-2 may interact with CD147 as they are both found in the same viral inclusion body. A quantification of this data would make the findings more robust.

Finally, the data in this paper lacks replicates, error bars, and statistics to show that the data are reproducible and statistically significant.

11.59.4 Significance

It has been shown in various studies that SARS-CoV-2 binds to the cell surface protein ACE2 for cell entry, yet ACE2 is highly expressed in heart, kidney, and intestinal cells, raising the concern that blocking ACE2 would result in harmful side effects [642] CD147 on the other hand is highly expressed in various tumor types, inflamed tissues, and pathogen infected cells, suggesting that the inhibition of CD147 would not result in major side effects [643,644] The research in this paper has resulted in an ongoing clinical trial in China to test the safety and efficacy of anti-CD147 Meplazumab to treat COVID-19. (ClinicalTrials.gov identifier NCT04275245).

11.59.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.60 Blood single cell immune profiling reveals that interferon-MAPK pathway mediated adaptive immune response for COVID-19

Huang et al. *medRxiv* [645]

11.60.1 Keywords

- COVID-19
- SARS-CoV-2
- PBMC
- single cell
- MAPK

11.60.2 Main Findings

The authors performed single-cell RNA sequencing (scRNAseq) of peripheral blood mononuclear cells isolated from whole blood samples of COVID-19 patients (n=10). Data was compared to scRNAseq of samples collected from patients with influenza A (n=1), acute pharyngitis (n=1), and cerebral infarction (n=1), as well as, three healthy controls. COVID-19 patients were categorized into those with moderate (n=6), severe (n=1), critical (n=1), and cured (n=2) disease. Analysis across all COVID-19 disease levels revealed 56 different cellular subtypes, among 17 immune cell types; comparisons between each category to the normal controls revealed **increased proportions of CD1c⁺ dendritic cells, CD8⁺ CTLs, and plasmacytoid dendritic cells and a decrease in proportions of B cells and CD4⁺ T cells.**

TCR sequencing revealed that greater clonality is associated with milder COVID-19 disease; BCR sequencing revealed that COVID-19 patients have circulating antibodies against known viral antigens, including EBV, HIV, influenza A, and other RNA viruses. This may suggest that the immune response to SARS-CoV-2 infection elicits production of antibodies against known RNA viruses.

Excluding enriched pathways shared by COVID-19 patients and patients with other conditions (influenza A, acute pharyngitis, and cerebral infarction), the authors identified the **interferon-MAPK**

signaling pathway as a major response to SARS-CoV-2 infection. The authors performed quantitative real-time reverse transcriptase polymerase chain reaction (RT-PCR) for interferon-MAPK signaling genes: *IRF27*, *BST2*, and *FOS*. These samples were collected from a separate cohort of COVID-19 patients (critical, n=3; severe, n=3; moderate, n=19; mild, n=3; and cured, n=10; and healthy controls, n=5). Notably, consistent with the original scRNAseq data, *FOS* showed up-regulation in COVID-19 patients and down-regulation in cured patients. **The authors propose that *FOS* may be a candidate marker gene for curative COVID-19 disease.**

11.60.3 Limitations

The sample size of this study is limited. To further delineate differences in the immune profile of peripheral blood of COVID-19 patients, a greater sample size is needed, and longitudinal samples are needed, as well. A better understanding of the immunological interactions in cured patients, for example, would require a profile before and after improvement.

Moreover, the conclusions drawn from this scRNAseq study point to potential autoimmunity and immune deficiency to distinguish different severities of COVID-19 disease. However, this requires an expanded number of samples and a more robust organization of specific immune cell subtypes that can be compared across different patients. Importantly, this criterion is likely needed to ensure greater specificity in identifying markers for COVID-19 infection and subsequent immune response.

11.60.4 Significance

At the single-cell level, COVID-19 disease has been characterized in the lung, but a greater understanding of systemic immunological responses is furthered in this study. Type I interferon is an important signaling molecule for the anti-viral response. The identification of the interferon-MAPK signaling pathway and the differential expression of MAPK regulators between patients of differing COVID-19 severity and compared to cured patients may underscore the importance of either immune deficiency or autoimmunity in COVID-19 disease.

11.60.5 Credit

This review was undertaken by Matthew D. Park as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.61 Cross-reactive antibody response between SARS-CoV-2 and SARS-CoV infection.

Lv et al. *bioRxiv* [[646](#)]

11.61.1 Keywords

SARS-CoV-2, SARS-CoV, spike protein, RBD, cross-reactivity, cross-neutralization, antibody, human patients, mouse

11.61.2 Main Findings

The authors explore the antigenic differences between SARS-CoV-2 and SARS-CoV by analyzing plasma samples from SARS-CoV-2 (n = 15) and SARS-CoV (n = 7) patients. Cross-reactivity in antibody binding to the spike protein between SARS-CoV-2 and SARS-CoV was found to be common, mostly targeting non-RBD regions in plasma from SARS-CoV-2 patients. Only one SARS-CoV-2 plasma sample was able

to cross-neutralize SARS-CoV, with low neutralization activity. No cross-neutralization response was detected in plasma from SARS-CoV patients.

To further investigate the cross-reactivity of antibody responses to SARS-CoV-2 and SARS-CoV, the authors analyzed the antibody response of plasma collected from mice infected or immunized with SARS-CoV-2 or SARS-CoV (n = 5 or 6 per group). Plasma from mice immunized with SARS-CoV-2 displayed cross-reactive responses to SARS-CoV S ectodomain and, to a lesser extent, SARS-CoV RBD. Similarly, plasma from mice immunized with SARS-CoV displayed cross-reactive responses to SARS-CoV-2 S ectodomain. Cross-neutralization activity was not detected in any of the mouse plasma samples.

11.61.3 Limitations

The size of each patient cohort is insufficient to accurately determine the frequency of cross-reactivity and cross-neutralization in the current SARS-CoV-2 pandemic. Recruitment of additional patients from a larger range of geographical regions and time points would also enable exploration into the effect of the genetic diversity and evolution of the SARS-CoV-2 virus on cross-reactivity. This work would also benefit from the mapping of specific epitopes for each sample. Future studies may determine whether the non-neutralizing antibody responses can confer *in vitro* protection or lead to antibody-dependent disease enhancement.

11.61.4 Significance

The cross-reactive antibody responses to S protein in the majority of SARS-CoV-2 patients is an important consideration for development of serological assays and vaccine development during the current outbreak. The limited extent of cross-neutralization demonstrated in this study indicates that vaccinating to cross-reactive conserved epitopes may have limited efficacy, presenting a key concern for the development of a more universal coronavirus vaccine to address the global health risk of novel coronavirus outbreaks.

11.61.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.62 The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study

Duan et al. *medRxiv* [[647](#)]

11.62.1 Keywords

- COVID-19
- SARS-CoV-2
- convalescent plasma
- treatment outcome
- pilot
- therapy
- transfusion

11.62.2 Main Findings

This is the first report to date of convalescent plasma therapy as a therapeutic against COVID-19 disease. This is a feasibility pilot study. The authors report the administration and clinical benefit of 200 mL of convalescent plasma (CP) (1:640 titer) derived from recently cured donors (CP selected among 40 donors based on high neutralizing titer and ABO compatibility) to 10 severe COVID-19 patients with confirmed viremia. The primary endpoint was the safety of CP transfusion. The secondary endpoint were clinical signs of improvement based on symptoms and laboratory parameters.

The authors reported use of methylene blue photochemistry to inactivate any potential residual virus in the plasma samples, without compromising neutralizing antibodies, and no virus was detected before transfusion.

The authors report the following:

- No adverse events were observed in all patients, except 1 patient who exhibited transient facial red spotting.
- All patients showed significant improvement in or complete disappearance of clinical symptoms, including fever, cough, shortness of breath, and chest pain after 3 days of CP therapy.
- Reduction of pulmonary lesions revealed by chest CT.
- Elevation of lymphocyte counts in patients with lymphocytopenia.
- Increase in SaO₂ in all patients, indicative of recuperating lung function.
- Resolution of SARS-CoV-2 viremia in 7 patients and increase in neutralizing antibody titers in 5 patients. Persistence of neutralizing antibody levels in 4 patients.

11.62.3 Limitations

It is important to note that most recipients had high neutralization titers of antibodies before plasma transfusion and even without transfusion it would be expected to see an increase in neutralizing antibodies over time. In addition to the small sample set number (n=10), there are additional limitations to this pilot study:

1. All patients received concurrent therapy, in addition to the CP transfusion. Therefore, it is unclear whether a combinatorial or synergistic effect between these standards of care and CP transfusion contributed to the clearance of viremia and improvement of symptoms in these COVID-19 patients.
2. The kinetics of viral clearance was not investigated, with respect to the administration of CP transfusion. So, the definitive impact of CP transfusion on immune dynamics and subsequent viral load is not well defined.
3. Comparison with a small historical control group is not ideal.

11.62.4 Significance

For the first time, a pilot study provides promising results involving the use of convalescent plasma from cured COVID-19 patients to treat others with more severe disease. The authors report that the administration of a single, high-dose of neutralizing antibodies is safe. In addition, there were encouraging results with regards to the reduction of viral load and improvement of clinical outcomes. It is, therefore, necessary to expand this type of study with more participants, in order to determine

optimal dose and treatment kinetics. It is important to note that CP has been studied to treat H1N1 influenza, SARS-CoV-1, and MERS-CoV, although it has not been proven to be effective in treating these infections.

11.62.5 Credit

Review by Matthew D. Park and revised by Alice O. Kamphorst and Maria A. Curotto de Lafaille as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.63 Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open label non-randomized clinical trial

[\[648\]](#)

11.63.1 Keywords

- hydroxychloroquine
- clearance
- viral load
- clinical trial

11.63.2 Main Findings

This study was a single-arm, open label clinical trial with 600 mg hydroxychloroquine (HCQ) in the treatment arm (n = 20). Patients who refused participation or patients from another center not treated with HCQ were included as negative controls (n = 16). Among the patients in the treatment arm, 6 received concomitant azithromycin to prevent superimposed bacterial infection. The primary endpoint was respiratory viral loads on day 6 post enrollment, measured by nasopharyngeal swab followed by real-time reverse transcription-PCR.

HCQ alone was able to significantly reduce viral loads by day 6 (n = 8/14, 57.1% complete clearance, $p < 0.001$); azithromycin appears to be synergistic with HCQ, as 6/6 patients receiving combined treatment had complete viral clearance ($p < 0.001$).

11.63.3 Limitations

Despite what is outlined above, this study has a number of limitations that must be considered. First, there were originally n = 26 patients in the treatment arm, with 6 lost to follow up for the following reasons: 3 transferred to ICU, 1 discharge, 1 self-discontinued treatment d/t side effects, and 1 patient expired. Total length of clinical follow up was 14 days, but the data beyond day 6 post-inclusion are not shown.

Strikingly, in supplementary table 1, results of the real-time RT-PCR are listed for the control and treatment arms from D0 – D6. However, the data are not reported in a standard way, with a mix of broadly positive or negative result delineation with Ct (cycle threshold) values, the standard output of real time PCR. It is impossible to compare what is defined as a positive value between the patients in the control and treatment arms without a standardized threshold for a positive test. Further, the starting viral loads reported at D0 in the groups receiving HCQ or HCQ + azithromycin were significantly different (ct of 25.3 vs 26.8 respectively), which could explain in part the differences observed in the response to treatment between 2 groups. Finally, patients in the control arm from outside the primary medical center in this study (Marseille) did not actually have samples tested by

PCR daily. Instead, positive test results from every other day were extrapolated to mean positive results on the day before and after testing as well (Table 2, footnote ^a).

Taken together, the results of this study suggest that HCQ represents a promising treatment avenue for COVID-19 patients. However, the limited size of the trial, and the way in which the results were reported does not allow for other medical centers to extrapolate a positive or negative result in the treatment of their own patients with HCQ +/- azithromycin. Further larger randomized clinical trials will be required to ascertain the efficacy of HCQ +/- azithromycin in the treatment of COVID-19.

11.63.4 Significance

Chloroquine is thought to inhibit viral infection, including SARS-Cov-2, by increasing pH within endosomes and lysosomes, altering the biochemical conditions required for viral fusion [278,649]. However, chloroquine also has immuno-modulatory effects that I think may play a role. Chloroquine has been shown to increase CTLA-4 expression at the cell surface by decreasing its degradation in the endo-lysosome pathway; AP-1 traffics the cytoplasmic tail of CTLA-4 to lysosomes, but in conditions of increased pH, the protein machinery required for degradation is less functional [650]. As such, more CTLA-4 remains in endosomes and is trafficked back to the cell surface. It is possible that this may also contribute to patient recovery via reduction of cytokine storm, in addition to the direct anti-viral effects of HCQ.

11.63.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.64 Recapitulation of SARS-CoV-2 Infection and Cholangiocyte Damage with Human Liver Organoids

[574]

11.64.1 Keywords

- CoVID-19
- 2019-nCoV
- SARS-CoV-2
- liver
- organoids
- Cholangiocyte

11.64.2 Main Findings

- Used human liver ductal organoids to determine ACE2+ cholangiocytes in healthy liver (2.92% of all cells) are infectable and support SARS-CoV-2 viral replication.
- Plaque-purified SARS-CoV-2 viral infection disrupted organoid barrier and bile transporting functions of cholangiocytes through dysregulation of genes involved in tight junction formation (CLDN1) and bile acid transportation (ASBT and CFTR).

11.64.3 Limitations:

- Unclear if liver damage observed in patients due to direct cholangiocyte infection or due to secondary immune/cytokine effects. This study argues for direct damage as it lacks immune contexture; but further studies needed with autopsy samples or organoid-immune cell co-culture to conclude strongly.
- Would be important to measure cholangiocyte-intrinsic anti-viral response and alarmins secreted upon infection, and furthermore study tropism of various immune cells to conditioned media from organoids infected with SARS-CoV-2.
- Does not address how cirrhotic liver or alcohol/smoking/obesity-associated liver organoids respond to SARS-CoV-2 infectivity and replication, worth pursuing to experimentally address clinical data indicating co-morbidities.

11.64.4 Significance

- Useful model to rapidly study drug activity against SARS-CoV-2 infection in liver, while monitoring baseline liver damage.
- Liver abnormality observed in >50% of CoVID-19 patients; the results from this study could explain the bile acid accumulation and consequent liver damage observed.

11.64.5 Credit

Review by Samarth Hegde as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.65 The sequence of human ACE2 is suboptimal for binding the S spike protein of SARS coronavirus 2

[[651](#)]

11.65.1 Keywords

- Coronavirus Disease 2019 (COVID-19)
- SARS-CoV-2
- Spike protein S
- ACE2

11.65.2 Main Findings

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infects cells through S spike glycoprotein binding angiotensin-converting enzyme (ACE2) on host cells. S protein can bind both membrane-bound ACE2 and soluble ACE2 (sACE2), which can serve as a decoy that neutralizes infection. Recombinant sACE2 is now being tested in clinical trials for COVID-19. To determine if a therapeutic sACE2 with higher affinity for S protein could be designed, authors generated a library containing every amino acid substitution possible at the 117 sites spanning the binding interface with S protein. The ACE2 library was expressed in human Expi293F cells and cells were incubated with medium containing the receptor binding domain (RBD) of SARS-CoV-2 fused to GFP. Cells with high or low affinity mutant ACE2 receptor compared to affinity of wild type ACE2 for the RBD were FACS sorted and transcripts from these sorted populations were deep sequenced. Deep mutagenesis identified numerous mutations in ACE2 that enhance RBD binding. This work serves to identify putative high affinity ACE2 therapeutics for the treatment of CoV-2.

11.65.3 Limitations

The authors generated a large library of mutated ACE2, expressed them in human Expi293F cells, and performed deep mutagenesis to identify enhanced binders for the RBD of SARS-CoV-2 S protein. While these data serve as a useful resource, the ability of the high affinity ACE2 mutants identified to serve as therapeutics needs further validation in terms of conformational stability when purified as well as efficacy/safety both *in vitro* and *in vivo*. Additionally, authors mentioned fusing the therapeutic ACE2 to Fc receptors to elicit beneficial host immune responses, which would need further design and validation.

11.65.4 Significance

This study identified structural ACE2 mutants that have potential to serve as therapeutics in the treatment of SARS-CoV-2 upon further testing and validation.

11.65.5 Credit

This review was undertaken by Katherine Lindblad and Tamar Plitt as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

Title: A serological assay to detect SARS-Cov-2 seroconversion in humans

Immunology keywords: specific serological assay - ELISA - seroconversion - antibody titers

Note: the authors of this review work in the same institution as the authors of the study

Main findings:

Production of recombinant whole Spike (S) protein and the smaller Receptor Binding Domain (RBD) based on the sequence of Wuhan-Hu-1 SARS-CoV-2 isolate. The S protein was modified to allow trimerization and increase stability. The authors compared the antibody reactivity of 59 banked human serum samples (non-exposed) and 3 serum samples from confirmed SARS-CoV-2 infected patients. All Covid-19 patient sera reacted to the S protein and RBD domain compared to the control sera.

The authors also characterized the antibody isotypes from the Covid-19 patients, and observed stronger IgG3 response than IgG1. IgM and IgA responses were also prevalent.

Limitations of the study:

The authors analyzed a total of 59 control human serum samples, and samples from only three different patients to test for reactivity against the RBD domain and full-length spike protein. It will be important to follow up with a larger number of patient samples to confirm the data obtained. Furthermore, it would be interesting to assess people at different age groups and determine whether unexposed control kids have a higher “background”.

Applications of the assay described in this study in diagnosis are limited, since antibody response should start to be detectable only one to two weeks after infection. Future studies will be required to assess how long after infection this assay allow to detect anti-CoV2 antibodies. Finally, while likely, the association of seroconversion with protective immunity against SARS-Cov-2 infection still needs to be fully established.

Relevance:

This study has strong implications in the research against SARS-CoV-2. First, it is now possible to perform serosurveys and determine who has been infected, allowing a more accurate estimate of infection prevalence and death rate. Second, if it is confirmed that re-infection does not happen (or is rare), this assay can be used as a tool to screen healthcare workers and prioritize immune ones to work with infected patients. Third, potential convalescent plasma donors can now be screened to help treating currently infected patients. Of note, this assay does not involve live virus handling. experimentally, this is an advantage as the assay does not require the precautions required by manipulation of live virus. Finally, the recombinant proteins described in this study represent new tools that can be used for further applications, including vaccine development.

11.66 COMPARATIVE PATHOGENESIS OF COVID-19, MERS AND SARS IN A NON-HUMAN PRIMATE MODEL

[\[652\]](#)

11.66.1 Keywords

- SARS-CoV2
- cynomolgus macaque
- SARS-CoV

11.66.2 Main Findings

This work assesses SARS-CoV-2 infection in young adult and aged cynomolgus macaques. 4 macaques per age group were infected with low-passage clinical sample of SARS-CoV-2 by intranasal and intratracheal administration. Viral presence was assessed in nose, throat and rectum through RT-PCR and viral culture. SARS-CoV-2 replication was confirmed in the respiratory track (including nasal samples), and it was also detected in ileum. Viral nucleocapsid detection by IHC showed infection of type I and II pneumocytes and epithelia. Virus was found to peak between 2 and 4 days after administration and reached higher levels in aged vs. young animals. The early peak is consistent with data in patients and contrasts to SARS-CoV replication. SARS-CoV-2 reached levels below detection between 8 and 21 days after inoculation and macaques established antibody immunity against the virus by day 14. There were histopathological alteration in lung, but no overt clinical signs. At day 4 post inoculation of SARS-CoV-2, two of four animals presented foci of pulmonary consolidation, with limited areas of alveolar edema and pneumonia, as well as immune cell infiltration. In sum, cynomolgus macaques are permissive to SARS-CoV-2 and develop lung pathology (less severe than SARS-CoV, but more severe than MERS-CoV).

11.66.3 Limitations

Even though cynomolgus macaques were permissive to SARS-CoV-2 replication, it is unclear if the viral load reaches levels comparable to humans and there wasn't overt clinical pathology.

11.66.4 Significance

The development of platforms in which to carry out relevant experimentation on SARS-CoV-2 pathophysiology is of great urgency. Cynomolgus macaques offer an environment in which viral replication can happen, albeit in a limited way and without translating into clinically relevant symptoms. Other groups are contributing to SARS-CoV2 literature using this animal model [\[639\]](#), potentially showing protection against reinfection in cured macaques. Therefore, this platform could

be used to examine SARS-CoV2 pathophysiology while studies in other animal models are also underway [[576](#),[653](#)].

11.66.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.67 Investigating the Impact of Asymptomatic Carriers on COVID-19 Transmission

[[654](#)]

11.67.1 Keywords

- Coronavirus Disease 2019 (COVID-19)
- SARS-CoV-2
- asymptomatic carriers
- mathematical model
- transmission

11.67.2 Main Findings

Multiple studies reported the same level of infectiousness between symptomatic and asymptomatic carriers of SARS-CoV-2. Given that asymptomatic and undocumented carriers escape public health surveillance systems, a better mathematical model of transmission is needed to determine a more accurate estimate of the basic reproductive number (R_0) of the virus to assess the contagiousness of virus. The authors developed a SEYAR dynamical model for transmission of the new coronavirus that takes into account asymptomatic and undocumented carriers. The model was validated using data reported from thirteen countries during the first three weeks of community transmission. While current studies estimate R_0 to be around 3, this model indicates that the value could range between 5.5 to 25.4.

11.67.3 Limitations

The SEYAR model realistically depicts transmission of the virus only during the initial stages of the disease. More data is necessary to better fit the model with current trends. In addition, multiple factors (e.g. behavioral patterns, surveillance capabilities, environmental and socioeconomic factors) affect transmission of the virus and so, these factors must be taken into consideration when estimating the R_0 .

11.67.4 Significance

Public health authorities use the basic reproductive number to determine the severity of disease. An accurate estimate of R_0 will inform intervention strategies. This model can be applied to different locations to assess the potential impact of COVID-19.

11.67.5 Credit

This review was undertaken by Tamar Plitt and Katherine Lindblad as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.68 Antibody responses to SARS-CoV-2 in COVID-19 patients: the perspective application of serological tests in clinical practice

Long et al. *medRxiv* [[655](#)]

11.68.1 Keywords

- Serum antibodies
- IgM
- IgG
- immunoassay
- diagnosis
- seroconversion

11.68.2 Main Findings

This study investigated the profile of the acute antibody response against SARS-CoV-2 and provided proposals for serologic tests in clinical practice. Magnetic Chemiluminescence Enzyme Immunoassay was used to evaluate IgM and IgG seroconversion in 285 hospital admitted patients who tested positive for SARS-CoV-2 by RT-PCR and in 52 COVID-19 suspected patients that tested negative by RT-PCR. A follow up study with 63 patients was performed to investigate longitudinal effects. In addition, IgG and IgM titers were evaluated in a cohort of close contacts (164 persons) of an infected couple.

The median day of seroconversion for both IgG and IgM was 13 days after symptom onset. Patients varied in the order of IgM/ IgG seroconversion and there was no apparent correlation of order with age, severity, or hospitalization time. This led the authors to conclude that for diagnosis IgM and IgG should be detected simultaneously at the early phase of infection.

IgG titers, but not IgM titers were higher in severe patients compared to non-severe patients after controlling for days post-symptom onset. Importantly, 12% of COVID-19 patients (RT-PCR confirmed) did not meet the WHO serological diagnosis criterion of either seroconversion or > 4-fold increase in IgG titer in sequential samples. This suggests the current serological criteria may be too stringent for COVID-19 diagnosis.

Of note, 4 patients from a group of 52 suspects (negative RT-PCR test) had anti-SARS-Cov-2 IgM and IgG. Similarly, 4.3% (7/162) of "close contacts" who had negative RT-PCR tests were positive for IgG and/or IgM. This highlights the usefulness of a serological assay to identify asymptomatic infections and/or infections that are missed by RT-PCR.

11.68.3 Limitations

This group's report generally confirms the findings of others that have evaluated the acute antibody response to SARS-Cov-2. However, these data would benefit from inclusion of data on whether the participants had a documented history of viral infection. Moreover, serum samples that were collected prior to SARS-Cov-2 outbreak from patients with other viral infections would serve as a useful negative control for their assay. Methodological limitations include that only one serum sample per case was tested as well as the heat inactivation of serum samples prior to testing. It has previously been reported that heat inactivation interferes with the level of antibodies to SARS-Cov-2 and their protocol may have resulted in diminished quantification of IgM, specifically [[656](#)].

11.68.4 Significance

Understanding the features of the antibody responses against SARS-CoV is useful in the development of a serological test for the diagnosis of COVID-19. This paper addresses the need for additional screening methods that can detect the presence of infection despite lower viral titers. Detecting the production of antibodies, especially IgM, which are produced rapidly after infection can be combined with PCR to enhance detection sensitivity and accuracy and map the full spread of infection in communities. Moreover, serologic assays would be useful to screen health care workers in order to identify those with immunity to care for patients with COVID19.

11.68.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.69 SARS-CoV-2 specific antibody responses in COVID-19 patients

[\[657\]](#)

11.69.1 Keywords

- immunoassay
- antibody specificity
- serology
- cross-reactivity

11.69.2 Main findings

Antibodies specific to SARS-CoV-2 S protein, the S1 subunit and the RBD (receptor-binding domain) were detected in all SARS-CoV-2 patient sera by 13 to 21 days post onset of disease. Antibodies specific to SARS-CoV N protein (90% similarity to SARS-CoV-2) were able to neutralize SARS-CoV-2 by PRNT (plaque reduction neutralizing test). SARS-CoV-2 serum cross-reacted with SARS-CoV S and S1 proteins, and to a lower extent with MERS-CoV S protein, but not with the MERS-CoV S1 protein, consistent with an analysis of genetic similarity. No reactivity to SARS-CoV-2 antigens was observed in serum from patients with ubiquitous human CoV infections (common cold) or to non-CoV viral respiratory infections.

11.69.3 Limitations

Authors describe development of a serological ELISA based assay for the detection of neutralizing antibodies towards regions of the spike and nucleocapsid domains of the SARS-CoV-2 virus. Serum samples were obtained from PCR-confirmed COVID-19 patients. Negative control samples include a cohort of patients with confirmed recent exposure to non-CoV infections (i.e. adenovirus, bocavirus, enterovirus, influenza, RSV, CMV, EBV) as well as a cohort of patients with confirmed infections with ubiquitous human CoV infections known to cause the common cold. The study also included serum from patients with previous MERS-CoV and SARS-CoV zoonotic infections. This impressive patient cohort allowed the authors to determine the sensitivity and specificity of the development of their in-house ELISA assay. Of note, seroconversion was observed as early as 13 days following COVID-19 onset but the authors were not clear how disease onset was determined.

11.69.4 Significance

Validated serological tests are urgently needed to map the full spread of SARS-CoV-2 in the population and to determine the kinetics of the antibody response to SARS-CoV-2. Furthermore, clinical trials are

ongoing using plasma from patients who have recovered from SARS-CoV-2 as a therapeutic option. An assay such as the one described in this study could be used to screen for strong antibody responses in recovered patients. Furthermore, the assay could be used to screen health care workers for antibody responses to SARS-CoV-2 as personal protective equipment continues to dwindle. The challenge going forward will be to standardize and scale-up the various in-house ELISA's being developed in independent laboratories across the world.

11.70 A brief review of antiviral drugs evaluated in registered clinical trials for COVID-19

Belhadi et al. [[658](#)]

11.70.1 Keywords

- Clinical trials
- COVID-19
- SARS CoV-2
- 2019-nCoV
- SARS Cov-2
- Hcov-19
- novel coronal virus
- new corona virus
- antiviral drugs

11.70.2 Main Findings

Summary of clinical trials registered as of March 7, 2020 from U.S, Chinese, Korean, Iranian and European registries. Out of the 353 studies identified, 115 were selected for data extraction. 80% of the trials were randomized with parallel assignment and the median number of planned inclusions was 63 (IRQ, 36-120). Most frequent therapies in the trials included; 1) antiviral drugs [lopinavir/ritonavir (n=15); umifenovir (n=9); favipiravir (n=7); redmesivir (n=5)]; 2) anti-malaria drugs [chloroquine (n=11); hydroxychloroquine (n=7)]; immunosuppressant drugs [methylprednisolone (n=5)]; and stem cell therapies (n=23). Medians of the total number of planned inclusions per trial for these therapies were also included. Stem cells and lopunavir/ritonavir were the most frequently evaluated candidate therapies (23 and 15 trials respectively), whereas remdesivir was only tested in 5 trials but these trials had the highest median number of planned inclusions per trial (400, IQR 394-453). Most of the agents used in the different trials were chosen based on preclinical assessments of antiviral activity against SARS CoV and MERS Cov corona viruses.

The primary outcomes of the studies were clinical (66%); virological (23%); radiological (8%); or immunological (3%). The trials were classified as those that included patients with severe disease only; trials that included patients with moderate disease; and trials that included patients with severe or moderate disease.

11.70.3 Limitations

The trials evaluated provided incomplete information: 23% of these were phase IV trials but the bulk of the trials (54%) did not describe the phase of the study. Only 52% of the trials (n=60) reported treatment dose and only 34% (n=39) reported the duration. A lot of the trials included a small number of patients and the trials are still ongoing, therefore no insight was provided on the outcome of the trials.

11.70.4 Significance

Nonetheless, this review serves as framework for identifying COVID-19 related trials, which can be expanded upon as new trials begin at an accelerated rate as the disease spreads around the world.

11.70.5 Credit

This review was undertaken by K Alexandropoulos as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.71 ACE-2 Expression in the Small Airway Epithelia of Smokers and COPD Patients: Implications for COVID-19

Leung et al. *medRxiv*. [[659](#)]

11.71.1 Keywords

- chronic obstructive pulmonary disease
- COPD
- smokingE-2
- risk factors

11.71.2 Main Findings

In bronchial epithelial samples from 3 different cohorts of individuals, ACE-2 gene expression was found to be significantly increased in both COPD patients and smokers relative to healthy controls. Across all test subjects, ACE-2 gene expression was also highly correlated with decreased forced expiratory volume in 1 second (FEV1), which may explain the increased COVID-19 disease severity in COPD patients. Former smokers were also found to show decreased ACE2 expression relative to current smokers and had no significant difference when compared to non-smokers.

11.71.3 Limitations

While the upregulation of ACE-2 is an interesting hypothesis for COVID-19 disease severity in COPD patients, this study leaves many more unanswered questions than it addresses. Further studies are required to show whether the specific cell type isolated in these studies is relevant to the pathophysiology of COVID-19. Furthermore, there is no attempt to show whether that increased ACE-2 expression contributes to greater disease severity. Does the increased ACE-2 expression lead to greater infectivity with SARS-CoV-2? There is no mechanistic explanation for why ACE-2 levels are increased in COPD patients. The authors could also have considered the impact of co-morbidities and interventions such as corticosteroids or bronchodilators on ACE-2 expression. Finally, given the extensive sequencing performed, the authors could have conducted significantly more in-depth analyses into gene signature differences.

11.71.4 Significance

This study attempts to address an important clinical finding that both smokers and COPD patients show increased mortality from COVID-19. The novel finding that ACE-2 expression is induced in smokers and COPD patients suggests not only a mechanism for the clinical observation, but also highlights the potential benefit of smoking cessation in reducing the risk of severe COVID-19 disease.

11.71.5 Credit

11.72 Dynamic profile of severe or critical COVID-19 cases

[[660](#)]

11.72.1 Keywords

- Coronavirus Disease 2019 (COVID-19)
- SARS-CoV-2
- progressive lymphopenia (PLD)
- T-lymphocytes
- clinical data
- co-infection
- influenza A

11.72.2 Main Findings

Authors evaluate clinical correlates of 10 patients (6 male and 4 female) hospitalized for severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). All patients required oxygen support and received broad spectrum antibiotics and 6 patients received anti-viral drugs. Additionally, 40% of patients were co-infected with influenza A. All 10 patients developed lymphopenia, two of which developed progressive lymphopenia (PLD) and died. Peripheral blood (PB) lymphocytes were analyzed – low CD4 and CD8 counts were noted in most patients, though CD4:CD8 ratio remained normal.

11.72.3 Limitations

The authors evaluated a small cohort of severe SARS-CoV-2 cases and found an association between T cell lymphopenia and adverse outcomes. However, this is an extremely small and diverse cohort (40% of patients were co-infected with influenza A). These findings need to be validated in a larger cohort. Additionally, the value of this data would be greatly increased by adding individual data points for each patient as well as by adding error bars to each of the figures.

11.72.4 Significance

This study provides a collection of clinical data and tracks evolution of T lymphocyte in 10 patients hospitalized for SARS-CoV-2, of which 4 patients were co-infected with influenza A.

11.72.5 Credit

This review was undertaken by Katherine Lindblad and Tamar Plitt as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.73 Association between Clinical, Laboratory and CT Characteristics and RT-PCR Results in the Follow-up of COVID-19 patients

Fu et al. *medRxiv*. [[661](#)]

11.73.1 Keywords

- COVID-19
- clinical
- lymphocyte
- CRP
- LDH
- HSST TNT
- PCR test
- readmission
- CT
- GGO
- disease progression

11.73.2 Study description

Data analyzed from 52 COVID-19 patients admitted and then discharged with COVID-19. Clinical, laboratory, and radiological data were longitudinally recorded with illness timecourse (PCR + to PCR-) and 7 patients (13.5%) were readmitted with a follow up positive test (PCR+) within two weeks of discharge.

11.73.3 Main Findings

- At admission:
 - The majority of patients had increased CRP at admission (63.5%).
 - LDH, and HSST TNT were significantly increased at admission.
 - Radiographic signs via chest CT showed increased involvement in lower lobes: right lower lobe (47 cases, 90.4%), left lower lobe (37 cases, 71.2%).
 - GGO (90.4%), interlobular septal thickening (42.3%), vascular enlargement (42.3%), and reticulation (11.5%) were most commonly observed.
- After negative PCR test (discharge):
 - CRP levels decreased lymphocyte counts (#/L) increased significantly (CD3+, CD3+/8+ and CD3+/4+) after negative PCR.
 - Consolidation and mixed GGO observed in longitudinal CT imaging w different extents of inflammatory exudation in lungs, with overall tendency for improvement (except 2/7 patients that were readmitted after discharge with re-positive test) after negative PCR.
- Seven patients repeated positive RT-PCR test and were readmitted to the hospital (9 to 17 day after initial discharge).
 - Follow up CT necessary to monitor improvement during recovery and patients with lesion progression should be given more attention.
 - Dynamic CT in addition to negative test essential in clinical diagnosis due to nasal swab PCR sampling bias (false-negatives).
 - Increase in CRP occurred in 2 readmitted patients (and decr. in lymphocytes in one patient), but was not correlated with new lesions or disease progression vs. improvement (very low N).

- Patients readmitted attributed to false-negative PCR vs. re-exposure.

11.73.4 Limitations

Patients sampled in this study were generally younger (65.4% < 50 yrs) and less critically ill/all discharged. Small number of recovered patients (N=18). Time of follow up was relatively short.. Limited clinical information available about patients with re-positive test (except CRP and lymph tracking).

11.73.5 Extended Results

NOTE: Patients sampled in this study were generally younger (65.4% < 50 yrs) and less critically ill/all discharged. After two consecutive negative PCR tests, patients were discharged.

Clinical Results at Admission

- Median interval disease onset to admission (5 days, IQR: 3-7)
- Most common symptoms included fever, fatigue, dry cough, and expectoration.
- Fifteen patients had reduced lymphocyte counts (28.8%).
- No change in WBC or Neutrophil counts.
- **The majority of patients had increased CRP at admission (63.5%).**
- **LDH, and HSST TNT were significantly increased at admission.**
- Fibrinogen was trending high though not significant.
- No major changes in liver function observed.
- **Radiographic signs via chest CT showed increased involvement in lower lobes: right lower lobe (47 cases, 90.4%), left lower lobe (37 cases, 71.2%).**
- **GGO (90.4%), interlobular septal thickening (42.3%), vascular enlargement (42.3%), and reticulation (11.5%) were most commonly observed.**

Change in Clinical Results following Negative Test

- **CRP levels decreased after negative PCR.**
- **Lymphocyte counts (#/L) increased significantly (CD3+, CD3+/8+ and CD3+/4+).**
- No significant change to CD4/8 ratio.
- LDH, HSST TNT, and Fibronegin remained high throughout, though range observed decreased over time.
- **Consolidation and mixed GGO observed in longitudinal CT imaging.**

- **Patients showed different extents of inflammatory exudation in lungs, with overall tendency for improvement (except 2/7 patients that were readmitted after discharge with re-positive test).**

Patients Readmitted with PCR+ test

- **Seven patients repeated positive RT-PCR test and were readmitted to the hospital (9 to 17 day after initial discharge).**
- Improvement during readmission in 4 patients and observation of segmental progression CT in 2 patients (2/18 or 11.1% - re-positive 9 and 10 days post-discharge).
- Two patients showed new GGO, while others improved greatly.
- **Follow up CT necessary to monitor improvement during recovery and patients with lesion progression should be given more attention.**
- **Dynamic CT in addition to negative test essential in clinical diagnosis due to nasal swab PCR sampling bias (false-negatives).**
- **Increase in CRP occurred in 2 readmitted patients (and decr. in lymphocytes in one patient), but was not correlated with new lesions or disease progression vs. improvement (very low N).**

11.73.6 Significance

Study tracked key clinical features associated with disease progression, recovery, and determinants of clinical diagnosis/management of COVID-19 patients.

11.73.7 Credit

This review was undertaken by Natalie Vaninov as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.74 An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 and multiple 2 endemic, epidemic and bat coronavirus

Sheahan et al. *bioRxiv*. [[662](#)]

11.74.1 Keywords

- Treatment
- Antiviral
- Broad spectrum antiviral
- ribonucleoside analog β -D-N4 30 hydroxycytidine (NHC)
- Remdesivir

11.74.2 Main Findings

β -D-N4 30 -hydroxycytidine (NHC, EIDD-1931) is an orally bioavailable ribonucleoside with antiviral activity against various RNA viruses including Ebola, Influenza and CoV. NHC activity introduced mutations in the viral (but not cellular) RNA in a dose dependent *manner* that directly correlated with

a decrease in viral titers. Authors show that NHC inhibited multiple genetically distinct Bat-CoV viruses in human primary epithelial cells *without affecting cell viability even at high concentrations (100 μ M)*. Prophylactic oral administration of NHC in C57BL/6 mice reduce lung titers of SARS-CoV and prevented weight loss and hemorrhage. Therapeutic administration of NHC in C57BL/6 mice 12 hours post infected with SARS-CoV reduced acute lung injury, viral titer, and lung hemorrhage. The degree of clinical benefit was dependent on the time of treatment initiation post infection. The authors also demonstrate that NHC reduces MERS-CoV infection titers, pathogenesis, and viral RNA in prophylactic and therapeutic settings.

11.74.3 Limitations

Most of the experiments were conducted using MERS-CoV, and SARS-CoV and a few experiments were conducted using other strains of CoV as opposed to SARS-CoV-2. The authors note the core residues that make up the RNA interaction sites (which constitutes the NHC interaction sites) are highly conserved among CoV and because of this conservation their understanding is that NHC can inhibit a broad-spectrum of CoV including SARS-CoV-2.

The increased viral mutation rates associated with NHC activity may have adverse effects if mutations cause the virus to become drug resistant, more infectious or speed-up immune evasion. *In addition, the temporal diminishing effectiveness of NHC on clinical outcome when NHC was used therapeutically is concerning. However, the longer window (7-10 days) for clinical disease onset in human patients from the time of infection compared to that of mice (24-48 hours), may associate with increased NHC effectiveness in the clinic.*

11.74.4 Significance

Prophylactic or therapeutic oral administration of NHC reduces lung titers and prevents acute lung failure in C57BL/6 mice infected with CoV. Given its *broad-spectrum antiviral activity, NHC could turn out to be a useful drug for treating current, emerging and future corona virus outbreaks.* #####
Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.75 Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs

Sangeun Jeon et al. [[663](#)]

11.75.1 Keywords

- COVID-19
- SARS CoV-2
- antiviral drugs
- niclosamide
- ciclesonide

11.75.2 Main Findings

A panel of ~3,000 FDA- and IND-approved antiviral drugs were previously screened for inhibitory efficacy against SARS CoV, a coronavirus related to the novel coronavirus SARS CoV-2 (79.5%) homology. 35 of these drugs along with another 15 (suggested by infectious disease specialists) were

tested in vitro for their ability to inhibit SARS CoV-2 infectivity of Vero cells while preserving cell viability. The infected cells were scored by immunofluorescence analysis using an antibody against the N protein of SARS CoV-2. Chloroquine, lopinavir and remdesivir were used as reference drugs.

Twenty four out of 50 drugs exhibited antiviral activity with IC₅₀ values ranging from 0.1-10µM. Among these, two stood out: 1) the anti helminthic drug niclosamide which exhibited potent antiviral activity against SARS CoV-2 (IC₅₀=0.28 µM). The broad-spectrum antiviral effect of niclosamide against SARS and MERS-CoV have been previously documented and recent evidence suggests that it may inhibit autophagy and reduce MERS CoV replication. 2) Ciclesonide, a corticosteroid used to treat asthma and allergic rhinitis, also exhibited antiviral efficacy but with a lower IC₅₀ (4.33µM) compared to niclosamide. The antiviral effects of ciclesonide were directed against NSP15, a viral ribonuclease which is the molecular target of this drug.

11.75.3 Limitations

The drugs were tested against SARS CoV-2 infectivity in vitro only, therefore preclinical studies in animals and clinical trials in patients will be needed for validation of these drugs as therapeutic agents for COVID-19. In addition, niclosamide exhibits low adsorption pharmacokinetically which could be alleviated with further development of drug formulation to increase effective delivery of this drug to target tissues. Nonetheless, niclosamide and ciclesonide represent promising therapeutic agents against SARS CoV-2 given that other compounds tested in the same study including favipiravir (currently used in clinical trials) and atazanavir (predicted as the most potent antiviral drug by AI-inference modeling) did not exhibit antiviral activity in the current study.

11.75.4 Credit

This review was undertaken by K Alexandropoulos as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.76 Respiratory disease and virus shedding in rhesus macaques inoculated with SARS-CoV-2

Munster et al. *bioRxiv*. [[664](#)]

11.76.1 Keywords

animal model, pulmonary infiltrates, dynamic of antibody response, cytokine

11.76.2 Main Findings

Inoculation of 8 Rhesus macaques with SARS-CoV-2, which all showed clinical signs of infection (respiratory pattern, reduced appetite, weight loss, elevated body temperature) resulting in moderate, transient disease. Four animals were euthanized at 3dpi, the 4 others at 21 dpi. Study of viral loads in different organs showed that nose swab and throat swabs were the most sensitive, with broncho-alveolar lavage. Interstitial pneumonia was visible in radiographies and at the histological scale too. Clinically, the macaques had similar symptoms as described in human patients with moderate disease.

Viral shedding was consistently detected in nose swabs and throat swabs immediately after infection but less consistent thereafter which could reflect virus administration route (intranasal, oral). Bronchoalveolar lavages performed as a measure of virus replication in the lower respiratory tract on animals maintained for 21 days, contained high viral loads in 1 and 3dpi. The majority of the animals

exhibited pulmonary edema and mild to moderate interstitial pneumonia on terminal bronchioles. In addition to the lung, viral RNA could also be detected throughout the respiratory track where viral replication mainly occurred.

Immunologic responses included leukocytosis, neutrophilia, monocytosis and lymphopenia in the majority of the animals at 1dpi. Lymphocytes and monocytes re-normalized at 2dpi. Neutrophils declined after 3dpi and through 10dpi after which they started to recover. After infection, serum analysis revealed significant increases in **IL1ra, IL6, IL10, IL15, MCP-1, MIP-1b, but quick normalization (3dpi). Antibody response started around 7dpi, and the antibody titers stayed elevated until 21dpi** (day of animal euthanasia).

11.76.3 Limitations

The macaques were inoculated via a combination of intratracheal, intranasal, ocular and oral routes, which might not reproduce how humans get infected. Maybe this can lead to different dynamics in the host immune response. Also, the authors noted that the seroconversion was not directly followed by a decline in viral loads, as observed in covid19 patients.

11.76.4 Significance

This work confirms that rhesus macaques can be a good model to study Covid-19, as it has been shown by other groups [[639](#),[652](#),[665](#)]. While these experiments recapitulate moderate COVID-19 in humans, the mode of inoculation via a combination of intratracheal, intranasal, ocular and oral routes, might not reproduce how humans get infected and may lead to different dynamics in the host immune response. For example, the authors noted that the seroconversion was not directly followed by a decline in viral loads, as observed in COVID-19 patients. Therefore, it will be interesting to follow their antibody titers longer and further assess the possibility/effect of reinfection in these macaques. It is essential to be able to understand the dynamic of the disease and associated immune responses, and to work on vaccine development and antiviral drug testing.

11.76.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.77 ACE2 Expression is Increased in the Lungs of Patients with Comorbidities Associated with Severe COVID-19

[[666](#)]

11.77.1 Keywords

- CoVID-19
- 2019-nCoV
- SARS-CoV-2
- lung
- comorbidities
- histone
- epigenetics

11.77.2 Main Findings

- Transcriptomic analysis using systems-level meta-analysis and network analysis of existing literature to determine ACE2 regulation in patients who have frequent COVID-19 comorbidities [eg- cardiovascular diseases, familial pulmonary hypertension, cancer].
- Enrichment analyses indicated pathways associated with inflammation, metabolism, macrophage autophagy, and ER stress.
- ACE2 higher in adenocarcinoma compared to adjacent normal lung; ACE2 higher in COPD patients compared to normal.
- Co-expression analysis identified genes important to viral entry such as RAB1A, ADAM10, HMGBs, and TLR3 to be associated with ACE2 in diseased lungs.
- ACE2 expression could be potentially regulated by enzymes that modify histones, including HAT1, HDAC2, and KDM5B.

11.77.3 Limitations:

- Not actual CoVID-19 patients with co-morbidities, so interpretations in this study need to be confirmed by analyzing upcoming transcriptomics from CoVID-19 patients having co-morbidity metadata.
- As mentioned by authors, study does not look at diabetes and autoimmunity as risk factors in CoVID-19 patients due to lack of data; would be useful to extend such analyses to those datasets when available.
- Co-expression analysis is perfunctory and needs validation-experiments especially in CoVID-19 lung samples to mean anything.
- Epigenomic analyses are intriguing but incomplete, as existence of histone marks does not necessarily mean occupancy. Would be pertinent to check cell-line data (CCLE) or actual CoVID-19 patient samples to confirm ACE2 epigenetic control.

11.77.4 Significance

- Study implies vulnerable populations have ACE2 upregulation that could promote CoVID-19 severity. Shows important data-mining strategy to find gene-networks associated with ACE2 upregulation in co-morbid patients.
- Several of the genes co-upregulated with ACE2 in diseased lung might play an important role in CoVID-19 and can be preliminary targets for therapeutics
- If in silico findings hold true, epigenetic control of ACE2 expression could be a new target for CoVID-19 therapy with strategies such as KDM5 demethylases.

11.77.5 Credit

Review by Samarth Hegde as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.78 Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial

11.78.1 Keywords

- Meplazumab
- CD147
- humanized antibody
- clinical trial

11.78.2 Main Findings

This work is based on previous work by the same group that demonstrated that SARS-CoV-2 can also enter host cells via CD147 (also called Basigin, part of the immunoglobulin superfamily, is expressed by many cell types) consistent with their previous work with SARS-CoV-1. ¹ A prospective clinical trial was conducted with 17 patients receiving Meplazumab, a humanized anti-CD147 antibody, in addition to all other treatments. 11 patients were included as a control group (non-randomized).

They observed a faster overall improvement rate in the Meplazumab group (e.g. at day 14 47% vs 17% improvement rate) compared to the control patients. Also, virological clearance was more rapid with median of 3 days in the Meplazumab group vs 13 days in control group. In laboratory values, a faster normalization of lymphocyte counts in the Meplazumab group was observed, but no clear difference was observed for CRP levels.

11.78.3 Limitations

While the results from the study are encouraging, this study was non-randomized, open-label and on a small number of patients, all from the same hospital. It offers evidence to perform a larger scale study. Selection bias as well as differences between treatment groups (e.g. age 51yo vs 64yo) may have contributed to results. The authors mention that there was no toxic effect to Meplazumab injection but more patient and longer-term studies are necessary to assess this.

11.78.4 Significance

These results seem promising as for now there are limited treatments for Covid-19 patients, but a larger cohort of patient is needed. CD147 has already been described to facilitate HIV [668], measles virus [669], and malaria [670] entry into host cells. This group was the first to describe the CD147-spike route of SARS-Cov-2 entry in host cells [641] p147. Indeed, they had previously shown in 2005 that SARS-Cov could enter host cells via this transmembrane protein [671]. Further biological understanding of how SARS-CoV-2 can enter host cells and how this integrates with ACE2R route of entry is needed. Also, the specific cellular targets of the anti-CD147 antibody need to be assessed, as this protein can be expressed by many cell types and has been shown to involved in leukocytes aggregation [672]. Lastly, Meplazumab is not a commercially-available drug and requires significant health resources to generate and administer which might prevent rapid development and use.

11.78.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.79 Potent human neutralizing antibodies elicited 1 by SARS-CoV-2 infection

11.79.1 Keywords

- monoclonal antibodies
- neutralization
- antibody cross-reactivity
- Receptor Binding Domain

11.79.2 Main Findings

In this study the authors report the affinity, cross reactivity (with SARS-CoV and MERS-CoV virus) and viral neutralization capacity of 206 monoclonal antibodies engineered from isolated IgG memory B cells of patients suffering from SARS-CoV-2 infection in Wuhan, China. All patients but one recovered from disease. Interestingly, the patient that did not recover had less SARS-CoV-2 specific B cells circulating compared to other patients.

Plasma from all patients reacted to trimeric Spike proteins from SARS-CoV-2, SARS-CoV and MERS-CoV but no HIV BG505 trimer. Furthermore, plasma from patients recognized the receptor binding domain (RBD) from SARS-CoV-2 but had little to no cross-reactivity against the RBD of related viruses SARS-CoV and MERS-CoV, suggesting significant differences between the RBDs of the different viruses. Negligible levels of cross-neutralization using pseudoviruses bearing Spike proteins of SARS-CoV-2, SARS-CoV or MERS-CoV, were observed, corroborating the ELISA cross-reactivity assays on the RBDs.

SARS-CoV-2 RBD specific B cells constituted 0.005-0.065% of the total B cell population and 0.023-0.329% of the memory subpopulation. SARS-CoV specific IgG memory B cells were single cell sorted to sequence the antibody genes that were subsequently expressed as recombinant IgG1 antibodies. From this library, 206 antibodies with different binding capacities were obtained. No discernible patterns of VH usage were found in the 206 antibodies suggesting immunologically distinct responses to the infection. Nevertheless, most high-binding antibodies were derived by clonal expansion. Further analyses in one of the patient derived clones, showed that the antibodies from three different timepoints did not group together in phylogenetic analysis, suggesting selection during early infection.

Using surface plasmon resonance (SPR) 13 antibodies were found to have 10^{-8} to 10^{-9} dissociation constants (Kd). Of the 13 antibodies, two showed 98-99% blocking of SARS-CoV-2 RBD-ACE2 receptor binding in competition assays. Thus, low Kd values alone did not predict ACE2 competing capacities. Consistent with competition assays the two antibodies that show high ACE2 blocking (P2C-2F6 and P2C-1F11) were the most capable of neutralizing pseudoviruses bearing SARS-CoV-2 spike protein (IC₅₀ of 0.06 and 0.03 µg/mL, respectively). Finally, using SPR the neutralizing antibodies were found to recognize both overlapping and distinct epitopes of the RBD of SARS-CoV-2.

11.79.3 Limitations

1. Relatively low number of patients
 - a. No significant conclusion can be drawn about the possible > correlation between humoral response and disease severity
2. *In vitro* Cytopathic Effect Assay (CPE) for neutralization activity
 - a. Huh7 cells were used in neutralization assays with > pseudoviruses, and they may not entirely mimic what happens in > the upper respiratory tract

b. CPE assay is not quantitative

3. Duplicated panel in Figure 4C reported (has been fixed in version 2)

11.79.4 Significance

This paper offers an explanation as to why previously isolated antibodies against SARS-CoV do not effectively block SARS-CoV-2. Also, it offers important insight into the development of humoral responses at various time points during the first weeks of the disease in small but clinically diverse group of patients. Furthermore, it provides valuable information and well characterized antibody candidates for the development of a recombinant antibody treatment for SARS-CoV-2. Nevertheless, it also shows that plasmapheresis might have variability in its effectiveness, depending on the donor's antibody repertoire at the time of donation.

11.79.5 Credit

Review by Jovani Catalan-Dibene as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.80 Characterisation of the transcriptome and proteome of SARS-CoV-2 using direct RNA sequencing and tandem mass spectrometry reveals evidence for a cell passage induced in-frame deletion in the spike glycoprotein that removes the furin-like cleavage site.

Davidson et al. [[673](#)]

11.80.1 Keywords

- Transcription
- RNA-seq
- proteomics
- mass spec
- furin cleavage site
- mutation
- pathogenicity

11.80.2 Main Findings

The authors performed long read RNA sequencing using an Oxford Nanopore MinION as well as tandem mass spec (MS) on Vero cells (a cell line derived from kidney cells of the African green monkey that is deficient in interferon) infected with SARS-CoV-2.

The authors found that passage of the virus in Vero cells gave rise to a spontaneous 9 amino acid deletion (679-NSPRRARSV-687 to I) in the spike (S) protein. The deleted sequence overlaps a predicted furin cleavage site at the S1 / S2 domain boundary that is present in SARS-CoV-2 but not SARS-CoV or the closely related bat coronavirus RaTG13, which are cleaved at S1 / S2 by other proteases [[39](#)]. Furin cleavage sites at similar positions in other viruses have been linked to increased pathogenicity and greater cell tropism [[674](#)]. Loss of this site in SARS-CoV-2 has also already been shown to increase viral entry into Vero but not BHK cells (which are also interferon deficient) [[46](#)]. The authors therefore make an important contribution in demonstrating that passage in Vero cells may lead to spontaneous loss of a key pathogenicity-conferring element in SARS-CoV-2.

11.80.3 Limitations

As the authors note, a similar study posted earlier by Kim et al., which also passaged SARS-CoV-2 in Vero cells, did not identify any loss in the S protein furin cleavage site [[675](#)]. It therefore remains to be determined how likely it is that this mutation spontaneously arises. A quantitative investigation using multiple experimental replicas to understand the spontaneous viral mutation rate at this site and elsewhere would be informative. Also, the mechanistic basis for the higher viral fitness conferred by loss of the furin cleavage site in Vero cells – but, evidently, not in vivo in humans, as this site is maintained in all currently sequenced circulating isolates - remains to be understood.

Due to the high base-call error rate of MinION sequencing, the authors' bioinformatic pipeline required aligning transcripts to a reference to correct sequencing artifacts. This presumably made it difficult or impossible to identify other kinds of mutations, such as single nucleotide substitutions, which may occur even more frequently than the deletions identified in this work. Pairing long read sequencing with higher-accuracy short-read sequencing may be one approach to overcome this issue.

11.80.4 Significance

As the authors suggest, animal studies using live virus challenge may need to periodically verify the genomic integrity of the virus, or potentially risk unknowingly using a likely less-pathogenic variant of the virus.

More broadly, the results emphasize the complexity and plasticity of the SARS-CoV-2 viral transcriptome and proteome. For example, the authors found multiple versions of transcripts encoding the nucleocapsid (N) protein, each with different small internal deletions, some of which were verified for translation by MS. A number of peptides arising from translation of unexpected rearrangements of transcripts were also detected. Additionally, the authors identified phosphorylation of a number of viral proteins (N, M, ORF 3a, nsp3, nsp9, nsp12 and S). For any cases where these have functional consequences, targeting the kinases responsible could be an avenue for drug development. Understanding the functional consequences of the mutations, transcript variations, and post translational modifications identified in this study will be important future work.

11.80.5 Credit

This review was undertaken by Tim O'Donnell, Maria Kuksin as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.81 A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug- Repurposing

Gordon et al. *bioRxiv* [[139](#)]

11.81.1 Keywords

- protein-protein interactions
- mass spectrometry
- drug targets

11.81.2 Main Findings

Gordon et al cloned, tagged and expressed 26 of the 29 SARS-CoV-2 proteins individually in HEK293T cells and used mass spectrometry to identify protein-protein interactions. They identified 332 viral-

host protein-protein interactions. Furthermore, they used these interactions to identify 66 existing drugs known to target host proteins or host pathways (eg SARS-CoV-2 N and Orf8 proteins interact with proteins regulated by the mTOR pathway, so mTOR inhibitors Silmitasertib and Rapamycin are possible drug candidates).

11.81.3 Limitations

The main limitation of the study stems from the reductionist model: overexpression of plasmids encoding individual viral proteins in HEK293T cells. This precludes any interactions between the viral proteins, or the combined effects of multiple proteins on the host, as they are expressed individually. Moreover, HEK293T cells come from primary embryonic kidney and therefore might not reflect how SARS-CoV-2 interacts with its primary target, the lung. However, the authors found that the proteins found to interact with viral proteins in their experiments are enriched in lung tissue compared to HEK293Ts.

11.81.4 Significance

The authors provide a “SARS-CoV-2 interaction map,” which may provide potential hypotheses as to how the virus interacts with the host. Further, they identified existing drugs that could disrupt these host-viral interactions and curb SARS-CoV-2 infection. Although these interactions have not been validated, this paper acts as a valuable resource.

11.81.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.82 First Clinical Study Using HCV Protease Inhibitor Danoprevir to Treat Naïve and Experienced COVID-19 Patients

Chen et al. *medRxiv*. [[676](#)]

11.82.1 Keywords

- Clinical study
- HCV protease inhibitor
- Danoprevir
- Ritonavir
- Covid19 treatment

11.82.2 Main Findings

The authors treated 11 Covid-19 patients with Danoprevir, a commercialized HCV protease inhibitor [[677](#)]^(p4), boosted by ritonavir [[678](#)], a CYP3A4 inhibitor (which enhances the plasma concentration and bioavailability of Danoprevir). Two patients had never received anti-viral therapy before (=naïve), whereas nine patients were on Lopinavir/Ritonavir treatment before switching to Danoprevir/Ritonavir (=experienced). The age ranged from 18 to 66yo.

Naïve patients that received Danoprevir/Ritonavir treatment had a decreased hospitalization time. Patients treated with Lopinavir/Ritonavir did not have a negative PCR test, while after switching to Danoprevir/Ritonavir treatment, the first negative PCR test occurred at a median of two days.

11.82.3 Limitations

The results of the study are very hard to interpret as there is no control group not receiving Danoprevir/Ritonavir treatment. This was especially true in naïve patients who seemed to have more mild symptoms before the start of the study and were younger (18 and 44yo) compared to the experienced patients (18 to 66yo). The possibility that the patients would have recovered without Danoprevir/Ritonavir treatment cannot be excluded.

11.82.4 Significance

The authors of the study treated patients with Danoprevir, with the rationale that this is an approved and well tolerated drug for HCV patients [678], and that it could also target the protease from SARS-CoV-2 (essential for viral replication and transcription). Indeed, homology modelling data indicated that HCV protease inhibitors have the highest binding affinity to Sars-Cov2 protease among other approved drugs [679].

While this study shows that the combination of Danoprevir and Ritonavir might be beneficial for Covid-19 patients, additional clinical trials with more patients and with better methodology (randomization and control group) are needed to make further conclusions.

11.82.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.83 Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial

[321]

11.83.1 Keywords

- hydroxychloroquine

11.83.2 Study Description

This is a randomized clinical trial of hydroxychloroquine (HCQ) efficacy in the treatment of COVID-19. From February 4 – February 28, 2020 142 COVID-19 positive patients were admitted to Renmin Hospital of Wuhan University. 62 patients met inclusion criteria and were enrolled in a double blind, randomized control trial, with 31 patients in each arm.

Inclusion criteria:

1. Age \geq 18 years
2. Positive diagnosis COVID-19 by detection of SARS-CoV-2 by RT-PCR
3. Diagnosis of pneumonia on chest CT
4. Mild respiratory illness, defined by $\text{SaO}_2/\text{SPO}_2$ ratio $> 93\%$ or $\text{PaO}_2/\text{FIO}_2$ ratio > 300 mmHg in hospital room conditions (Note: relevant clinical references described below.)

- a. Hypoxia is defined as an SpO₂ of 85-94%; severe hypoxia < 85%.
 - b. The PaO₂/FIO₂ (ratio of arterial oxygen tension to fraction of inspired oxygen) is used to classify the severity of acute respiratory distress syndrome (ARDS). Mild ARDS has a PaO₂/FIO₂ of 200-300 mmHg, moderate is 100-200, and severe < 100.
5. Willing to receive a random assignment to any designated treatment group; not participating in another study at the same time

Exclusion criteria:

1. Severe or critical respiratory illness (not explicitly defined, presumed to be respiratory function worse than outlined in inclusion criteria); or participation in trial does not meet patient's maximum benefit or safe follow up criteria
2. Retinopathy or other retinal diseases
3. Conduction block or other arrhythmias
4. Severe liver disease, defined by Child-Pugh score \geq C or AST > twice the upper limit
5. Pregnant or breastfeeding
6. Severe renal failure, defined by eGFR \leq 30 mL/min/1.73m², or on dialysis
7. Potential transfer to another hospital within 72h of enrollment
8. Received any trial treatment for COVID-19 within 30 days before the current study

All patients received the standard of care: oxygen therapy, antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids. Patients in the HCQ treatment group received additional oral HCQ 400 mg/day, given as 200 mg 2x/day. HCQ was administered from days 1-5 of the trial. The primary endpoint was 5 days post enrollment or a severe adverse reaction to HCQ. The primary outcome evaluated was time to clinical recovery (TTCR), defined as return to normal body temperature and cough cessation for > 72h. Chest CT were imaged on days 0 and 6 of the trial for both groups; body temperature and patient reports of cough were collected 3x/day from day 0 – 6. The mean age and sex distribution between the HCQ and control arms were comparable.

11.83.3 Main Findings

There were 2 patients showing mild secondary effects of HCQ treatment. More importantly, while 4 patients in the control group progressed to severe disease, none progressed in the treatment group.

TTCR was significantly decreased in the HCQ treatment arm; recovery from fever was shortened by one day (3.2 days control vs. 2.2 days HCQ, $p = 0.0008$); time to cessation of cough was similarly reduced (3.1 days control vs. 2.0 days HCQ, $p = 0.0016$).

Overall, it appears that HCQ treatment of patients with mild COVID-19 has a modest effect on clinical recovery (symptom relief on average 1 day earlier) but may be more potent in reducing the progression from mild to severe disease.

11.83.4 Limitations

This study is limited in its inclusion of only patients with mild disease, and exclusion of those on any treatment other than the standard of care. It would also have been important to include the laboratory values of positive RT-PCR detection of SARS-CoV-2 to compare the baseline and evolution of the patients' viral load.

11.83.5 Limitations

Despite its limitations, the study design has good rigor as a double blind RCT and consistent symptom checks on each day of the trial. Now that the FDA has approved HCQ for treatment of COVID-19 in the USA, this study supports the efficacy of HCQ use early in treatment of patients showing mild symptoms, to improve time to clinical recovery, and possibly reduce disease progression. However, most of the current applications of HCQ have been in patients with severe disease and for compassionate use, which are out of the scope of the findings presented in this trial. Several additional clinical trials to examine [hydroxychloroquine](#) are now undergoing; their results will be critical to further validate these findings.

11.83.6 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

Structure-based modeling of SARS-CoV-2 peptide/HLA-A02 antigens

<https://doi.org/10.1101/2020.03.23.004176>

Immunology keywords:

CoVID-19, 2019-nCoV, SARS-CoV-2, comparative, homology, peptide, modeling, simulation, HLA-A, antigen

Summary of Findings:

- The authors utilize homology modeling to identify peptides from the SARS-CoV-2 proteome that potentially bind HLA-A*02:01.
- They utilize high-resolution X-ray structures of peptide/MHC complexes on Protein Data Bank, substitute homologous peptides with SARS-CoV-2 peptides, and calculate MHC/SARS-CoV-2 peptide Rosetta binding energy.
- They select MHC/SARS-CoV-2 complex models with highest binding energy for further study and publish models in an online database (<https://rosettamhc.chemistry.ucsc.edu>).

Limitations:

- The authors only utilize computational methods and predicted SARS-CoV-2 peptides must be validated experimentally for immunogenicity and clinical response.
- Due to computational burden and limited availability of high resolution X-ray structures on PDB, authors only simulate 9-mer and 10-mer peptide binding to HLA-A*02:01.
- Since the authors compare select existing X-ray structures as a starting point, backbone conformations that deviate significantly between test and template peptides are not captured.

Furthermore, Rosetta modeling protocols do not capture all possible structures and binding energy scoring does not fully recapitulate fundamental forces.^{1,2}

Importance/Relevance:

- The authors identify and publish high-scoring SARS-CoV-2 peptides that may direct a targeted, experimental validation approach toward a COVID-19 vaccine.
- The authors utilize Rosetta simulation to further filter results from NetMHCpan 4.0, supporting machine learning prediction with structural analysis.
- The authors develop RosettaMHC, a computationally efficient method of leveraging existing X-ray structures for identification of immunogenic peptides.

References:

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Review by Jonathan Chung as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn school of medicine, Mount Sinai.

11.84 Serology characteristics of SARS-CoV-2 infection since the exposure and post symptoms onset

Lou et al. *medRxiv*. [[680](#)]

11.84.1 Keywords

- Seroconversion rate
- Total Antibody
- Ab
- IgG and IgM
- antibody

11.84.2 Main Findings

Currently, the diagnosis of SARS-CoV-2 infection entirely depends on the detection of viral RNA using polymerase chain reaction (PCR) assays. False negative results are common, particularly when the samples are collected from upper respiratory. Serological detection may be useful as an additional testing strategy. In this study the authors reported that a typical acute antibody response was induced during the SARS-CoV-2 infection, which was discussed earlier¹. The seroconversion rate for Ab, IgM and IgG in COVID-19 patients was 98.8% (79/80), 93.8% (75/80) and 93.8% (75/80), respectively. The first detectable serology marker was total antibody followed by IgM and IgG, with a median seroconversion time of 15, 18 and 20 days-post exposure (d.p.e) or 9, 10- and 12-days post-onset (d.p.o). Seroconversion was first detected at day 7d.p.e in 98.9% of the patients. Interestingly they found that viral load declined as antibody levels increased. This was in contrast to a previous study [[621](#)],

showing that increased antibody titers did not always correlate with RNA clearance (low number of patient sample).

11.84.3 Limitations

Current knowledge of the antibody response to SAR-CoV-2 infection and its mechanism is not yet well elucidated. Similar to the RNA test, the absence of antibody titers in the early stage of illness could not exclude the possibility of infection. A diagnostic test, which is the aim of the authors, would not be useful at the early time points of infection but it could be used to screen asymptomatic patients or patients with mild disease at later times after exposure.

11.84.4 Significance

Understanding the antibody responses against SARS-CoV2 is useful in the development of a serological test for the diagnosis of COVID-19. This manuscript discussed acute antibody responses which can be deducted in plasma for diagnostic as well as prognostic purposes. Thus, patient-derived plasma with known antibody titers may be used therapeutically for treating COVID-19 patients with severe illness.

11.84.5 Credit

This review was undertaken and edited by Konstantina A as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.85 SARS-CoV-2 launches a unique transcriptional signature from in vitro, ex vivo, and in vivo systems

Blanco-Melo et al. *bioRxiv*. [[681](#)]

11.85.1 Keywords

- host cellular response
- host-pathogen interaction
- type I interferon
- type III interferon
- inflammation
- RNA-seq
- comparative analysis

11.85.2 Main Findings

Given the high mortality rate of SARS-CoV-2 relative to other respiratory viruses such seasonal IAV and RSV, there may be underlying host-pathogen interactions specific to SARS-CoV-2 that predispose to a worse clinical outcome. Using *in vivo*, *ex vivo*, and *in vitro* systems, the authors profiled host cell transcriptional responses to SARS-CoV-2 and to other common respiratory viruses (seasonal IAV and RSV). SARS-CoV-2 infection *in vitro* led to an induction of type I interferon response signaling and the upregulation of cytokine/chemokines transcripts. In comparison with IAV and RSV infection, SARS-CoV-2 *in vitro* appears to uniquely induce less type I and type III interferon expression and higher levels of two cytokines previously implicated in respiratory inflammation. Lastly, *in vivo* data from ferrets showed a reduced induction of cytokines and chemokines by SARS-CoV-2 infection relative to IAV infection.

11.85.3 Limitations

While these results are promising, there are several key weaknesses of this paper. 1) As the authors point out, there is an undetectable level of SARS-CoV-2 putative receptor (ACE2) and protease (TMPRSS2) expression in the lung epithelial cell line used for the *in vitro* studies. This raises the important question of whether viral replication actually occurs in any of the models used, which may explain the lack of interferon production observed *in vitro* in SARS-CoV-2 treated cells. Further studies characterizing viral titers across timepoints are needed. 2) Furthermore, these studies only characterize the host response at a single dose and timepoint per virus, and it is unclear why these doses/timepoints were chosen. This leaves open the possibility that the observed differences between viruses could be due to differences in dose, timing, host response, or a combination of all of these. 3) It is unclear whether ferrets are productively infected, which cell types are infected, and the extent/timing of the clinical course of infection. Moreover, the *in vitro* and *in vivo* data do not strongly correlate and the reasons for this are unclear.

11.85.4 Significance

This paper describes potentially unique transcriptional signatures of host cells exposed to SARS-CoV-2. If validated, these findings may help explain clinical outcomes and could be targeted in future therapeutic interventions.

11.85.5 Potential Conflicts of Interest Disclosure

The reviewers are also researchers at the Icahn School of Medicine at Mount Sinai.

11.85.6 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.86 A New Predictor of Disease Severity in Patients with COVID-19 in Wuhan, China

Zhou et al. *bioRxiv*. [[682](#)]

11.86.1 Keywords

- disease severity
- clinical data
- Neutrophils/lymphocytes ratio
- CRP
- D-dimer

11.86.2 Main Findings

377 hospitalized patients were divided into two groups: severe and non-severe pneumonia. The laboratory results of their first day of admission were retrospectively analyzed to identify predictors of disease severity.

After adjusting for confounding factors from chronic comorbidities (such as high blood pressure, type 2 diabetes, coronary heart disease, and chronic obstructive pulmonary disease), the independent risk

factors identified for severe pneumonia were **age**, the **ratio of neutrophil/lymphocytes counts**, **CRP** and **D-dimer** levels.

To further increase the specificity and sensibility of these markers, they showed that their multiplication **[(Neutrophil/lymphocyte count) * CRP * D-dimer]** was a better predictor of disease severity, with higher sensitivity (95.7%) and specificity (63.3%), with a cutoff value of 2.68.

11.86.3 Limitations

This study included 377 hospitalized patients. Among them, 45.6% patients tested positive for SARS-Cov-2 nucleic acid test results, and others were included in the study based on clinically diagnosis even if the molecular diagnosis was negative. Thus, additional studies are needed to verify this on a larger number of covid-19 certified patients and the cutoff value might be adjusted. Also, all the patients that did not have the clinical characteristics of severe pneumonia were included in the non-severe pneumonia group, but usually patients are also divided into moderate and mild disease.

Also, studying different subset of lymphocytes could lead to a more specific predictor. Another study showed that the neutrophils to CD8+ T cells ratio was a strong predictor of disease severity [591]. Another more precise study showed that the percentage of helper T cells and regulatory T cells decrease but the percentage of naïve helper T cells increases in severe cases [584]. Taking these subpopulations into account might make the predictor more powerful.

Other studies also noted an inverse correlation between disease severity and LDH [625] or IL6 [634] levels, but the authors here do not discuss LDH nor IL6 levels, although this could help to strengthen the predictor.

The study is based on the results obtained on the first day of admission, studying the dynamic of the changes in patients might also be interesting to better predict disease severity.

11.86.4 Significance

This study confirms that the neutrophil to lymphocyte ratio can be a predictor of disease severity as shown by many others [583,584,598]. The novelty here is that they show that a combination with other markers can enhance the specificity and sensibility of the predictor, although the study could be improved by taking into account sub-populations of lymphocytes and more biological factors from patients such as LDH and IL6.

11.86.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.87 Metabolic disturbances and inflammatory dysfunction predict severity of coronavirus disease 2019 (COVID-19): a retrospective study

Shuke Nie et al. *medRxiv*. [683]

11.87.1 Keywords

- metabolism
- fasting blood glucose
- serum total protein

- albumin
- blood lipid
- HDL-C
- APOA1
- lymphocytopenia
- IL-6
- CRP
- severity prediction of COVID19

11.87.2 Main Findings

Retrospective Study on 97 COVID-19 hospitalized patients (25 severe and 72 non-severe) analyzing clinical and laboratory parameter to predict transition from mild to severe disease based on more accessible indicators (such as fasting blood glucose, serum protein or blood lipid) than inflammatory indicators. In accordance with other studies, age and hypertension were risk factors for disease severity, and lymphopenia and increased IL-6 was observed in severe patients. The authors show that fasting blood glucose (FBG) was altered and patients with severe disease were often hyperglycemic. Data presented support that hypoproteinaemia, hypoalbuminemia, and reduction in high-density lipoprotein (HDL-C) and ApoA1 were associated with disease severity.

11.87.3 Limitations

In this study non-severe patients were divided in two groups based on average course of the disease: mild group1 (14 days, n=28) and mild group 2 (30 days, n=44). However mild patients with a longer disease course did not show an intermediate phenotype (between mild patients with shorter disease course and severe patients), hence it is unclear whether this was a useful and how it impacted the analysis. Furthermore, the non-exclusion of co-morbidity factors in the analysis may bias the results (e.g. diabetic patients and glucose tests) It is not clear at what point in time the laboratory parameters are sampled. In table 3, it would have been interesting to explore a multivariate multiple regression. The correlation lacks of positive control to assess the specificity of the correlation to the disease vs. correlation in any inflammatory case. The dynamic study assessing the predictability of the laboratory parameter is limited to 2 patients. Hence there are several associations with disease severity, but larger studies are necessary to test the independent predictive value of these potential biomarkers.

11.87.4 Significance

As hospital are getting overwhelmed a set of easily accessible laboratory indicators (such as serum total protein) would potentially provide a triage methodology between potentially severe cases and mild ones. This paper also opens the question regarding metabolic deregulation and COVID-19 severity.

11.87.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.88 Viral Kinetics and Antibody Responses in Patients with COVID-19

[684]

11.88.1 Keywords

- CoVID-19
- 2019-nCoV
- SARS-CoV-2
- IgG
- IgM
- clinical
- kinetics
- antibodies

11.88.2 Main Findings

- Prospective cohort of 67 patients, clinical specimens taken and follow-up conducted.
- Viral shedding, serum IgM, IgG antibody against NP evaluated and correlated to disease severity and clinical outcome
- Viral RNA levels peaked at 1 week from febrile/cough symptom onset in sputum, nasal swabs, and stool samples. Shedding ranged from 12-19 days (median ranges) and was longer in severe patients.
- IgM and IgG titers stratified patients into three archetypes as 'strong vs weak vs non-responders'. Strong responders (with higher IgM/IgG titers) were significantly higher in severe patients.

11.88.3 Limitations

Specific for immune monitoring.

- Not clear if stool RNA captured from live infection in intestine/liver or from swallowed sputum. Transmission electron microscopy (TEM) carried out on sputum samples as proof of concept, but not stools. TEM unreasonable for actual clinical diagnosis.
- Several patients had co-morbidities (such as pulmonary and liver disease) that were not accounted for when tracking antibody responses. Viral kinetics and IgM/IgG titers in subsets of patients with underlying conditions/undergoing certain medication would be informative.

11.88.4 Significance

- Three archetypes of antibody response to SARS-CoV-2 with different disease progression and kinetics is useful to stratify patients, and for future serological tests.
- Strong spike-IgG levels often correlate with lymphopenia and CoVID-19 disease severity [685], similar to macaque studies in SARS [502]. It would be critical to see if anti-NP or anti-Spike IgG antibodies for SARS-CoV-2 also elicit similar detrimental effects before clinical use.

11.88.5 Credit

Review by Samarth Hegde as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.89 COVID-19 infection induces readily detectable morphological and inflammation-related phenotypic changes in peripheral blood monocytes, the severity of which correlate with patient outcome

11.89.1 Keywords

- Monocytes
- FSC-high
- PBMC
- ACE2
- inflammatory cytokines

11.89.2 Main Findings

This study is based on flow cytometry immunophenotyping of PBMCs from 28 patients diagnosed positive for SARS-Cov2 (COVID19). The authors identify a population of abnormally large (FSC-hi) monocytes, present in COVID19 patients, but absent in PBMCs of healthy volunteers (n=16) or patients with different infections (AIDS, malaria, TB). This FSC-hi monocytic population contains classical, intermediate and non-classical (monocytes (based on CD14 and CD16 expression) that produce inflammatory cytokines (IL-6, TNF and IL-10). The authors suggest an association of FSC-hi monocytes with poor outcome and correlate a high percentage of FSC-low monocytes, or higher ratio of FSC-low/hi monocytes, with faster hospital discharge.

11.89.3 Limitations

While identification of the monocytic population based on FSC is rather robust, the characterization of these cells remains weak. A comprehensive comparison of FSC-hi monocytes with FSC-low monocytes from patients and healthy controls would be of high value. It is unclear if percentages in blood are among CD45+ cells. Furthermore, it would have been important to include absolute numbers of different monocytic populations (in table 1 there are not enough samples and it is unclear what the authors show).

The authors show expression of the ACE2 receptor on the surface of the monocytes, and highlight these cells as potential targets of SARS-Cov2. However, appropriate controls are needed. CD16 has high affinity to rabbit IgG and it is unclear whether the authors considered unspecific binding of rabbit anti-ACE2 to Fc receptors. Gene expression of ACE-2 on monocytes needs to be assessed. Furthermore, it would be important to confirm infection of monocytes by presence of viral proteins or viral particles by microscopy.

Considering the predictive role of FSC-hi monocytes on the development of the disease and its severity, some data expected at this level are neither present nor addressed. Although the cohort is small, it does include 3 ICU patients. What about their ratio of FSC-low vs FSC-hi monocytes in comparison to other patients? Was this apparent early in the disease course? Does this population of FSC-hi monocytes differ between ICU patients and others in terms of frequency, phenotype or cytokine secretion?

In general, figures need to be revised to make the data clear. For example, in Fig. 5, according to the legend it seems that patients with FSC-high monocytes are discharged faster from the hospital. However according to description in the text, patients were grouped in high or low levels of FSC-low monocytes.

11.89.4 Significance

Despite the limitations of this study, the discovery of a FSC-high monocyte population in COVID-19 patients is of great interest. With similar implication, a the recent study by Zhou et al. [589] identified a connection between an inflammatory CD14+CD16+ monocyte population and pulmonary immunopathology leading to deleterious clinical manifestations and even acute mortality after SARS-CoV-2 infections. Although the presence of these monocytes in the lungs has yet to be demonstrated, such results support the importance of monocytes in the critical inflammation observed in some COVID19 patients.

11.89.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.90 Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study

Miller et al. *medRxiv*. [687]

11.90.1 Keywords

- BCG vaccine
- epidemiology
- vaccination policy

11.90.2 Main Findings

The authors compared middle and high income countries that never had a universal BCG vaccination policy (Italy, Lebanon, Nederland, Belgium) and countries with a current policy (low income countries were excluded from the analysis as their number of cases and deaths might be underreported for the moment). **Countries that never implement BCG vaccination have a higher mortality rate than countries which have a BCG vaccination policy** (16.38 deaths per million people vs 0.78). Next, **the authors show that an earlier start of vaccination correlates with a lower number of deaths per million inhabitants**. They interpret this as the vaccine protecting a larger fraction of elderly people, which are usually more affected by COVID-19. Moreover, higher number of COVID-19 **cases** were presented in countries that never implemented a universal BCG vaccination policy.

11.90.3 Limitations

While this study aims to test an intriguing hypothesis unfortunately, the data is not sufficient at this time to accurately make any determinations. Several caveats must be noted including: not all countries are in the same stage of the pandemic, the number of cases/deaths is still changing very rapidly in a lot of countries and thus the association may only reflect exposure to the virus. This analysis would need to be re-evaluated when all the countries are passed the pandemic and more accurate numbers are available. Additionally, very few middle and high-income countries ever implemented universal BCG vaccination, which can be a source of bias (5 countries, vs 55 that have a BCG vaccine policy). Effective screening and social isolation policies also varied considerable across the countries tested and may reflect another important confounder. The authors could consider analyzing the Case Fatality Rate (CFR, % of patients with COVID-19 that die), to more correct for exposure although testing availability will still bias this result. Variability in mortality within countries or cities with variable vaccination and similar exposure could also be appropriate although confounders will still be present.

11.90.4 Significance

BCG vaccine is a live attenuated strain derived from *Mycobacterium bovis* and used for a vaccine for tuberculosis (TB). This vaccine has been proven to be efficient in preventing childhood meningitis TB, but doesn't prevent adult TB as efficiently. For this reason, several countries are now only recommending this vaccine for at-risk population only.

This study shows that there is a correlation between BCG vaccination policy and reduced mortality for Covid-19. Indeed, BCG vaccine has been shown to protect against several viruses and enhance innate immunity [688], which could explain why it could protect against SARS-CoV-2 infection, but the exact mechanism is still unknown. **Moreover, the efficiency of adult/older people vaccination and protection against Covid-19 still needs to be assessed.** Regarding this, Australian researchers are starting a clinical trial of BCG vaccine for healthcare workers [689], to assess if it can protect them against Covid-19.

11.90.5 Credit

This review was undertaken as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.91 Non-neural expression of SARS-CoV-2 entry genes in the olfactory epithelium

[690]

11.91.1 Keywords

- CoVID-19
- 2019-nCoV
- SARS-CoV-2
- anosmia
- olfaction
- scRNAseq

11.91.2 Main Findings

- Study analyzed bulk and scRNAseq data of olfactory cell types from publicly-available mouse, nonhuman primate and human datasets.
- show that *ACE2* and *TMPRSS2* (genes involved in SARS-CoV-2 entry) are expressed in olfactory epithelial (OE) cells, basal stem cells and respiratory epithelium (RE), but not sensory neurons.
- Comparison of human RE and OE datasets (Deprez et al. 2019; Durante et al. 2020) revealed that *ACE2* and *TMPRSS2* expression in OE sustentacular cells was similar to expression in the remainder of the non-nasal respiratory tract.

11.91.3 Limitations

- Transcript data alone from healthy respiratory/olfactory cells is not sufficient to confirm infectivity of nasal passage, or to indicate damage to epithelia.

- No mechanism defined for anosmia; it is not clear if epithelial injury leads to reduced sensitivity or increased inflammation and altered immune contexture drives neural/epithelial dysfunction. Will be critical to test this in CoVID-19 patient samples or mouse models.

11.91.4 Significance

- Study provides possible rationale for anosmia observed in several CoVID-19 patients.
- Raises possibility that nasal respiratory goblet, ciliated cells, and olfactory epithelia may serve as a viral reservoir after initial SARS-CoV-2 infection.
- Human olfactory sensory neurons express several other molecules important to CoV (not CoV-19) entry such as *FURIN*, *ST6GAL1*, *ST3GAL4*; this suggests wider mechanism of neuronal infectivity in other coronaviruses.

11.91.5 Credit

Review by Samarth Hegde as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

Title:

SARS-CoV-2 proteome microarray for mapping COVID-19 antibody interactions at amino acid resolution

Immunology keywords: SARS-CoV-2, COVID-19, high throughput, peptide microarray, antibody epitope screening

The main finding of the article:

This study screened the viral protein epitopes recognized by antibodies in the serum of 10 COVID-19 patients using a new SARS-CoV-2 proteome peptide microarray. The peptide library was constructed with 966 linear peptides, each 15 amino acids long with a 5 amino acid overlap, based on the protein sequences encoded by the genome of the Wuhan-Hu-1 strain.

To investigate crossreactivity between SARS-CoV-1 and SARS-CoV-2, they tested rabbit monoclonal and polyclonal antibodies against SARS-CoV-1 nucleocapsid (N) in the microarray. Antibodies against SARS-CoV-1 N displayed binding to the SARS-CoV-2 nucleocapsid (N) peptides. Polyclonal antibodies showed some crossreactivity to other epitopes from membrane (M), spike (S), ORF1ab and ORF8. This suggests that previous exposure to SARS-CoV-1 may induced antibodies recognizing both viruses.

Screening of IgM and IgG antibodies from 10 COVID-19 patients showed that many antibodies targeted peptides on M, N, S, Orf1ab, Orf3a, Orf7a, and Orf8 from SARS-CoV-2, while immunodominant epitopes with antibodies in more than 80 % COVID-19 patients were present in N, S and Orf3. It is shown that the receptor binding domain (RBD) resides on S protein and RBD is important for SARS-CoV-2 to enter the host cells via ACE2. Among six epitopes on S protein, structural analysis predicted that three epitopes were located at the surface and three epitopes were located inside of the protein. Furthermore, some IgM antibodies from 1 patient and IgG antibodies from 2 patients bound to the same epitope (residue 456-460, FRKSN) which resided within the RBD, and structural analysis determined that this epitope was located in the region of the RBD loop that engages with ACE2.

Critical analysis of the study:

In addition to the limitations mentioned in the manuscript, it would have been informative to do the analysis over the course of the disease. The pattern of antibody recognition, especially on S protein, and the course of antibodies of different isotypes recognizing the same peptide might correlate to the clinical course in these patients. It would also have been informative to analyze the presence of cross-reactive antibodies from patients previously exposed to SARS-CoV-1.

The importance and implications for the current epidemics:

This study identified linear immunodominant epitopes on SARS-CoV-2, Wuhan-Hu-1 strain. This is a valuable information to design vaccines that will elicit desirable immune responses.

The Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Directly Decimates Human Spleens and Lymph Nodes

Review by Matthew D. Park

Revised by Miriam Merad

Keywords: COVID-19, SARS-CoV-2, spleen, lymph node, ACE2, macrophage

Main findings

It has been previously reported that COVID-19 patients exhibit severe lymphocytopenia, but the mechanism through which this depletion occurs has not been described. In order to characterize the cause and process of lymphocyte depletion in COVID-19 patients, the authors performed gross anatomical and *in situ* immune-histochemical analyses of spleens and lymph nodes (hilar and subscapular) obtained from post-mortem autopsies of 6 patients with confirmed positive viremia and 3 healthy controls (deceased due to vehicle accidents).

Primary gross observations noted significant splenic and LN atrophy, hemorrhaging, and necrosis with congestion of interstitial blood vessels and large accumulation of mononuclear cells and massive lymphocyte death. They found that CD68⁺ CD169⁺ cells in the spleens, hilar and subscapular LN, and capillaries of these secondary lymphoid organs expressed the ACE2 receptor and stain positive for the SARS-CoV-2 nucleoprotein (NP) antigen, while CD3⁺ T cells and B220⁺ B cells lacked both the ACE2 receptor and SARS-CoV-2 NP antigen. ACE2⁺ NP⁺ CD169⁺ macrophages were positioned in the splenic marginal zone (MZ) and in the marginal sinuses of LN, which suggests that these macrophages were positioned to encounter invading pathogens first and may contribute to virus dissemination.

Since SARS-CoV-2 does not directly infect lymphocytes, the authors hypothesized that the NP⁺ CD169⁺ macrophages are responsible for persistent activation of lymphocytes via Fas::FasL interactions that would mediate activation-induced cell death (AICD). Indeed, the expression of Fas was significantly higher in virus-infected tissue than that of healthy controls, and TUNEL staining showed significant lymphocytic apoptosis. Since pro-inflammatory cytokines like IL-6 and TNF- α can also engage cellular apoptosis and necrosis, the authors interrogated the cytokine expression of the secondary lymphoid organs from COVID-19 patients; IL-6, not TNF- α , was elevated in virus-infected splenic and lymph node tissues, compared to those of healthy controls, and immunofluorescent staining showed that IL-6 is primarily produced by the infected macrophages. *In vitro* infection of THP1 cells with SARS-CoV-2 spike protein resulted in selectively increased *Il6* expression, as opposed to *Il1b* and *Tnfa* transcription. Collectively, the authors concluded that a combination of Fas up-regulation and IL-6 production by NP⁺ CD169⁺ macrophages induce AICD in lymphocytes in secondary lymphoid organs, resulting in lymphocytopenia.

In summary, this study reports that CD169⁺ macrophages in the splenic MZ, subscapular LN, and the lining capillaries of the secondary lymphoid tissues express ACE2 and are susceptible to SARS-CoV-2 infection. The findings point to the potential role of these macrophages in viral dissemination, immunopathology of these secondary lymphoid organs, hyperinflammation and lymphopenia.

Limitations

Technical

A notable technical limitation is the small number of samples (n=6); moreover, the analysis of these samples using multiplexed immunohistochemistry and immunofluorescence do not necessarily provide the depth of unbiased interrogation needed to better identify the cell types involved.

Biological

The available literature and ongoing unpublished studies, including single-cell experiments of spleen and LN from organ donors, do not indicate that ACE2 is expressed by macrophages; however, it remains possible that ACE2 expression may be triggered by type I IFN in COVID-19 patients. Importantly, the SARS-CoV-2 NP staining of the macrophages does not necessarily reflect direct infection of these macrophages; instead, positive staining only indicates that these macrophages carry SARS-CoV-2 NP as antigen cargo, which may have been phagocytosed. Direct viral culture of macrophages isolated from the secondary lymphoid organs with SARS-CoV-2 is required to confirm the potential for direct infection of macrophages by SARS-CoV-2. Additionally, it is important to note that the low to negligible viremia reported in COVID-19 patients to-date does not favor a dissemination route via the blood, as suggested by this study, which would be necessary to explain the presence of virally infected cells in the spleen.

Relevance

Excess inflammation in response to SARS-CoV-2 infection is characterized by cytokine storm in many COVID-19 patients. The contribution of this pathology to the overall fatality rate due to COVID-19, not even necessarily directly due to SARS-CoV-2 infection, is significant. A better understanding of the full effect and source of some of these major cytokines, like IL-6, as well as the deficient immune responses, like lymphocytopenia, is urgently needed. In this study, the authors report severe tissue damage in spleens and lymph nodes of COVID-19 patients and identify the role that CD169⁺ macrophages may play in the hyperinflammation and lymphocytopenia that are both characteristic of the disease. It may, therefore, be important to note the effects that IL-6 inhibitors like Tocilizumab and Sarilumab may specifically have on splenic and LN function. It is important to note that similar observations of severe splenic and LN necrosis and inflammation in patients infected with SARS-CoV-1 further support the potential importance and relevance of this study.

11.92 Cigarette smoke triggers the expansion of a subpopulation of respiratory epithelial cells that express the SARS-CoV-2 receptor ACE2

[\[691\]](#)

11.92.1 Keywords

- CoVID-19
- 2019-nCoV
- SARS-CoV-2
- respiration

- cigarette
- ACE2
- lung

11.92.2 Main Findings

- Study uses scRNAseq, bulk seq data and air-liquid interface culture experiments to show that cigarette smoke causes a dose-dependent upregulation of ACE2 in mouse and human lungs (transplantation, tumor resection, or IPF datasets).
- ACE2 was not up-regulated in patients with asthma or lung-sarcoidosis or in mouse models of cystic fibrosis or carcinogen exposure.
- Cathepsin B (alternate protease involved in viral entry) is increased in smoke-exposed mouse or human lungs.
- Smoke triggers a protective expansion of mucus-secreting MUC5AC+ goblet and SCGB1A1+ club cells; ACE2 presence in these cells is increased upon smoke exposure.

11.92.3 Limitations:

- Long-term smokers usually have several co-morbidities including immune dysfunction, which can affect interpretation of CoV-2 susceptibility in these datasets. Ideally, analyses can control for major co-morbidities across smokers and non-smokers (immune suppression, cardiovascular disease and atherosclerosis).
- Hyperplasia of ACE2+ goblet cells upon smoking needs to be separated from ACE2 upregulation in existing goblet cells.
- ACE2 expression increase alone does not confirm increased viral entry into goblet cells; future studies with air-liquid interface cultures testing CoV-2 infectivity in *ex vivo* epithelial cells from human epithelial lines, *ex vivo* samples or hACE2 mice will be very informative.

11.92.4 Significance

- This study may partially explain why smokers are more likely to develop severe SARS-CoV-2 infections. Also, the reversibility of ACE2 expression upon smoking cessation suggests that quitting smoking could lessen CoV-2 susceptibility.
- Absence of ACE2 upregulation in other lung inflammation pathologies implies CoV-2 susceptibility might be smoking-specific, and not fibrosis-specific.
- Another preprint showed ACE2 expression increases in lung of patients with CoV-2 co-morbidities such as hypertension [666]; these studies collectively paint a better picture of CoV-2 susceptibility before actual experiments can be carried out.

11.92.5 Credit

Review by Samarth Hegde as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

11.93 The comparative superiority of IgM-IgG antibody test to real-time reverse transcriptase PCR detection for SARS-CoV-2 infection diagnosis

Liu et al. *medRxiv*. [[692](#)]

11.93.1 Keywords

- IgM/IgG antibody test
- nucleic acid test
- SARS-CoV-2 detection

11.93.2 Main Findings

The study compares IgM and IgG antibody testing to RT-PCR detection of SARS-CoV-2 infection. 133 patients diagnosed with SARS-CoV-2 in Renmin Hospital (Wuhan University, China) were analyzed. The positive ratio was 78.95% (105/133) in IgM antibody test (SARS-CoV-2 antibody detection kit from YHLO Biotech) and 68.42% (91/133) in RT-PCR (SARS-CoV-2 ORF1ab/N qPCR detection kit). There were no differences in the sensitivity of SARS-CoV-2 diagnosis in patients grouped according to disease severity. For example, IgG responses were detected in 93.18% of moderate cases, 100% of severe cases and 97.3% of critical cases. In sum, positive ratios were higher in antibody testing compared to RT-PCR detection, demonstrating a higher detection sensitivity of IgM-IgG testing for patients hospitalized with COVID-19 symptoms.

11.93.3 Limitations

This analysis only included one-time point of 133 hospitalized patients, and the time from symptom onset was not described. There was no discussion about specificity of the tests and no healthy controls were included. It would be important to perform similar studies with more patients, including younger age groups and patients with mild symptoms as well as asymptomatic individuals. It is critical to determine how early after infection/symptom onset antibodies can be detected and the duration of this immune response.

11.93.4 Significance

The IgM-IgG combined testing is important to improve clinical sensitivity and diagnose COVID-19 patients. The combined antibody test shows higher sensitivity than individual IgM and IgG tests or nucleic acid-based methods, at least in patients hospitalized with symptoms.

11.93.5 Credit

Review by Erica Dalla as part of a project by students, postdocs and faculty at the Immunology Institute of the Icahn School of Medicine, Mount Sinai.

Title: Lectin-like Intestinal Defensin Inhibits 2019-nCoV Spike binding to ACE2

Immunology keywords: defensins, spike protein, intestinal Paneth cells, ACE2 binding

Main Findings:

Human ACE2 was previously identified as the host receptor for SARS-CoV-2. Despite ACE2 being expressed in both lung alveolar epithelial cells and small intestine enterocytes, respiratory problems are the most common symptom after viral infection while intestinal symptoms are much less

frequent. Thus, the authors here investigate the biology behind the observed protection of the intestinal epithelium from SARS-CoV-2. Human defensin 5 (HD5), produced by Paneth cells in the small intestine, was shown to interact with human ACE2, with a binding affinity of 39.3 nM by biolayer interferometry (BLI). A blocking experiment using different doses of HD5 coating ACE2 showed that HD5 lowered viral spike protein S1 binding to ACE2. Further, a molecular dynamic simulation demonstrated a strong intermolecular interaction between HD5 and the ACE2 ligand binding domain. To test HD5 inhibitory effect on S1 binding to ACE2, human intestinal epithelium Caco-2 cells were preincubated with HD5. Preincubation strongly reduced adherence of S1 to surface of cells. HD5 was effective at a concentration as low as 10 µg/mL, comparable to the concentration found in the intestinal fluid.

Limitations:

The study focuses exclusively on intestinal cells. However, HD5 could have been tested to block ACE2-S1 binding in human lung epithelial cells as a potential treatment strategy. It would be useful to know whether HD5 could also prevent viral entry in lung cells.

Relevance:

This work provides the first understanding of the different efficiency of viral entry and infection among ACE2-expressing cells and tissues. Specifically, the authors show that human defensin 5 produced in the small intestine is able to block binding between S1 and ACE2 necessary for viral entry into cells. The study provides a plausible explanation on why few patients show intestinal symptoms and suggests that patients with intestinal disease that decrease defensins' production may be more susceptible to SARS-CoV-2. It also indicates that HD5 could be used as a molecule to be exogenously administered to patients to prevent viral infection in lung epithelial cells.

Title:

Susceptibility of ferrets, cats, dogs and different domestic animals to SARS-coronavirus-2

Immunology keywords: SARS-CoV-2, ferret, cat, laboratory animal, domestic animals

The main finding of the article:

This study evaluated the susceptibility of different model laboratory animals (ferrets), as well as companion (cats and dogs), and domestic animals (pigs, chickens and ducks) to SARS-CoV-2. They tested infection with two SARS-CoV2 isolates, one from an environmental sample collected in the Huanan Seafood Market in Wuhan (F13-E) and the other from a human patient in Wuhan (CTan-H).

Ferrets were inoculated with either of the two viruses by intranasal route with 10^5 pfu, and the viral replication was evaluated. Two ferrets from each group were euthanized on day 4 post infection (p.i.). At day 4 p.i., viral RNA and infectious viruses were detected only in upper respiratory tract (nasal turbinate, upper palate, tonsils, but not in the trachea, lungs or other tissues). Viral RNA and virus titer in the remaining ferrets were monitored in nasal washes and rectal swabs on days 2, 4, 6, 8 and 10 p.i. Viral RNA and infectious viruses were detected in nasal washes until day 8 p.i. One ferret in each group developed fever and loss of appetite on days 10 and 12 p.i., however, viral RNA was practically undetectable. These two ferrets showed severe lymphoplasmacytic perivascularitis and vasculitis in the lungs and lower antibody titers compared to other 4 ferrets.

Cats. Five subadult 8-month-old domestic cats were inoculated with CTan-h virus and three uninfected cats were placed in a cage adjacent to each of the infected cats to monitor respiratory droplet transmission. Viral RNA was detected in the upper respiratory organs from all infected cats and in one

out of three exposed cats. All infected (inoculated and exposed) cats developed elevated antibodies against SARS-CoV2. Viral replication studies with juvenile cats (70-100 days) revealed massive lesions in the nasal and tracheal mucosa epithelium and lungs of two inoculated cats which died or were euthanized on day 3 p.i., and infection in one out of three exposed cats. These results indicated SARS-CoV2 could replicate in cats, that juvenile cats were more susceptible than adults, and that SARS-CoV2 could be transmitted via respiratory droplets between cats.

Dogs and others. Five 3-month-old beagle dogs were inoculated and housed with two uninoculated beagles in a room. Two virus inoculated dogs seroconverted, but others including two contact dogs were all seronegative for SARS-CoV2 and infectious virus was not detected in any swabs collected. Viral RNA was not detected in swabs from pigs, chickens, and ducks inoculated or contacted. These results indicated that dogs, pigs, chickens, and ducks might have low or no susceptibility to SARS-CoV2.

Critical analysis of the study:

This manuscript describes the viral replication and clinical symptoms of SARS-CoV2 infection in ferrets, and the SARS-CoV2 infection and transmission in cats. Clinical and pathological analysis was not performed in cats, therefore the correlation of virus titer with symptoms severity in the adult and juvenile cats could not be determined.

The importance and implications for the current epidemics:

SARS-CoV-2 transmission to tigers, cats and dogs has been previously reported. It should be noted that this manuscript did not evaluate the transmission from cats to human. Nevertheless, it clearly showed higher susceptibility of ferrets and domestic cats to SARS-CoV-2. This data strongly indicates the need for surveillance of possible infection and transmission of SARS-CoV-2 by domestic cats.

11.94 Virus-host interactome and proteomic survey of PMBCs from COVID-19 patients reveal potential virulence factors influencing SARS-CoV-2 pathogenesis

Li et al. *bioRxiv*. [[140](#)]

11.94.1 Keywords

- PBMC
- virulence factors – interaction network – nsp9
- nsp10 – NKRF

11.94.2 Main findings

The authors identified **intra-viral protein-protein interactions** (PPI) with two different approaches: genome wide yeast-two hybrid (Y2H) and co-immunoprecipitation (co-IP). A total of 58 distinct PPI were characterized. A screen of **viral-host PPI** was also established by overexpressing all the SARS-CoV-2 genes with a Flag epitope into HEK293 cells and purifying each protein complex. Interacting host proteins were then identified by liquid chromatography and tandem mass spectrometry. 251 cellular proteins were identified, such as subunits of ATPase, 40S ribosomal proteins, T complex proteins and proteasome related proteins, for a total of 631 viral-host PPI. Several interactions suggesting protein-mediated modulation of the immune response were identified, highlighting the multiple ways SARS-CoV-2 might reprogram infected cells.

Subsequently, the authors compared global proteome profiles of PBMCs from healthy donors (n=6) with PBMC from COVID-19 patients with mild (n=22) or severe (n=13) symptoms. 220 proteins were found to be differentially expressed between *healthy donors and mild COVID-19 patients*, and a pathway analysis showed **a general activation of the innate immune response**. 553 proteins were differentially expressed between the PBMC of *mild and severe COVID-19 patients*, most of them (95%) being downregulated in severe patients. Functional pathway analysis indicated a defect of T cell activation and function in severe COVID-19. There was also evidence suggesting reduced antibody secretion by B cells. Together, these results suggest a **functional decline of adaptive immunity**. A FACS analysis of PBMC from severe patients indicated higher levels of IL6 and IL8 but not IL17 compared to mild patients.

Finally, the authors focused on NKRF, an endogenous repressor of IL8/IL6 synthesis that was previously identified as interacting with SARS-Cov-2 nsp9,10,12,13 and 15. Individually expressed nsp9 and nsp10 (but not nsp12, nsp13, nsp15) induced both IL6 and IL8 in lung epithelial A459 cells, indicating that nsp9 and nsp10 may be directly involved in the induction of these pro-inflammatory cytokines. The authors finally argue that nsp9 and nsp10 represent potential drug targets to prevent over-production of IL6 and IL8 in infected cells, and reducing the over-activation of neutrophils.

11.94.3 Limitations

First, the authors seem to have forgotten to include the extended data in the manuscript, and their proteomic data does not seem to be publicly available for the moment, which limits greatly our analysis of their results.

While this work provides important data on host and viral PPI, only 19 interactions were identified by Y2H system but 52 with co-IP. The authors do not comment about what could lead to such differences between the two techniques and they don't specify whether they detected the same interactions using the two techniques.

Moreover, the PBMC protein quantification was performed comparing bulk PBMC. Consequently, protein differences likely reflect differences in cell populations rather than cell-intrinsic differences in protein expression. While this analysis is still interesting, a similar experiment performed on pre-sorted specific cell populations would allow measuring proteome dynamics at a higher resolution.

Finally, the authors did not discuss their results in regards to another SARS-CoV-2 interactome of host-viral PPI that had been published previously¹. This study reported 332 host-virus PPI, but no interaction of viral proteins with NKRF was found. Some interactions were found in both studies (eg. N and G3BP1, Orf6 and RAE1). However, the time point used to lyse the cells were different (40h previously vs 72h here), which could explain some of the differences.

11.94.4 Relevance

The identification of many interactions between intra-viral and host-virus PPI provides an overview of host protein and pathways that are modulated by SARS-CoV-2, which can lead to the identification of potential targets for drug development.

In the model proposed by the authors, nsp9 and nsp10 from SARS-Cov-2 induce an over-expression of IL6 and IL8 by lung epithelial cells, which recruits neutrophils and could lead to an excess in lung infiltration. Nsp9 has been shown to be essential for viral replication for SARS-Cov-1², and shares a 97% homology with nsp9 from SARS-Cov-2³. Further, nsp9 crystal structure was recently solved³, which can help to develop drug inhibitors if this protein is further confirmed as being important for the virulence of SARS-Cov-2.

1. Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug-Repurposing. *bioRxiv*. March 2020:2020.03.22.002386. doi:10.1101/2020.03.22.002386
2. Miknis ZJ, Donaldson EF, Umland TC, Rimmer RA, Baric RS, Schultz LW. Severe acute respiratory syndrome coronavirus nsp9 dimerization is essential for efficient viral growth. *J Virol*. 2009;83(7):3007-3018. doi:10.1128/JVI.01505-08
3. Littler DR, Gully BS, Colson RN, Rossjohn J. *Crystal Structure of the SARS-CoV-2 Non-Structural Protein 9, Nsp9*. Molecular Biology; 2020. doi:10.1101/2020.03.28.013920

Title: Prediction and Evolution of B Cell Epitopes of Surface Protein in SARS-CoV-2

Keywords: SARS-CoV-2; Epitopes; Bioinformatics; Evolution

Summary/Main findings:

Lon et al. used a bioinformatic analysis of the published SARS-CoV-2 genomes in order to identify conserved linear and conformational B cell epitopes found on the spike (S), envelope (E), and membrane (M) proteins. The characterization of the surface proteins in this study began with an assessment of the peptide sequences in order to identify hydrophilicity indices and protein instability indices using the Port-Param tool in ExPASy. All three surface proteins were calculated to have an instability score under 40 indicating that they were stable. Linear epitopes were identified on the basis of surface probability and antigenicity, excluding regions of glycosylation. Using BepiPred 2.0 (with a cutoff value of 0.35) and ABCpred (with a cutoff value of 0.51), 4 linear B cell epitopes were predicted for the S protein, 1 epitope for the E protein, and 1 epitope for the M protein. For structural analysis, SARS-CoV assemblies published in the Protein Data Bank (PDB) acting as scaffolds for the SARS-CoV-2 S and E amino acid sequences were used for input into the SWISS-MODEL server in order to generate three-dimensional structural models for the assessment of conformational epitopes. Using Ellipro (cutoff value of 0.063) and SEPPA (cutoff value of 0.5), 1 conformational epitope was identified for the S protein and 1 epitope was identified for the E protein, both of which are accessible on the surface of the virus. Finally, the Consurf Server was used to assess the conservation of these epitopes. All epitopes were conserved across the published SARS-CoV-2 genomes and one epitope of the spike protein was predicted to be the most stable across coronavirus phylogeny.

Critical Analysis/Limitations:

While this study provides a preliminary identification of potential linear and conformational B cell epitopes, the translational value of the epitopes described still needs extensive experimental validation to ascertain whether these elicit a humoral immune response. The conformational epitope analyses are also limited by the fact that they are based off of predicted 3D structure from homology comparisons and not direct crystal structures of the proteins themselves. Additionally, since there was not a published M protein with a high homology to SARS-CoV-2, no conformational epitopes were assessed for this protein. Finally, while evolutionary conservation is an important consideration in understanding the biology of the virus, conservation does not necessarily imply that these sites neutralize the virus or aid in non-neutralizing *in vivo* protection.

Relevance/Implications:

With further experimental validation that confirms that these epitopes induce effective antibody responses to the virus, the epitopes described can be used for the development of treatments and vaccines as well as better characterize the viral structure to more deeply understand pathogenesis.