COVID-19 Therapeutics – A landscape analysis using systematic reviews and clinical data

by

Elvis Shehu

BA, Biochemistry, Ithaca College (2000)
MS, Bioinformatics, Northeastern University (2004)

SUBMITTED TO THE SYSTEM DESIGN AND MANAGEMENT PROGRAM IN PARTIAL FUFILLMENT OF THE REQURIEMENTS FOR DEGREE IN

MASTERS OF SCIENCE IN ENGINEERING AND MANAGEMENT
AT THE
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

June 2021

Signature of Author: _____
System Design & Management Program
February 19th, 2021

Certified by: _____
Stan N. Finkelstein, MD
Senior Research Scientist, IDSS
Thesis Supervisor

Accepted by: _____
Joan S. Rubin
Executive Director, System Design & Management Program

This page has been intentionally left blank

Acknowledgements

My deepest gratitude goes to my thesis advisor, Professor Stan Finkelstein, for initially helping me to brainstorm and identify a thesis topic and later on for guiding me throughout the stages of researching and writing it – Thank you Prof. Stan!

Many heartfelt thanks go to Joan Rubin, who welcomed me to the MIT family even before the first day on campus and who has always provided me with the outmost support and advice. I would also like to thank Bill Foley, Amal Elalam, Prof. Oliver de Weck, Dr. Bryan Moser, Dr. Bruce Cameron, Pat Hale, and all the other wonderful faculty and staff that make MIT the special place it is. Many thanks also to all of my teachers over the years – yours is a noble profession.

A big shoutout and thanks goes to all my fellow MIT and Sloan classmates – you are some of the most incredibly resourceful individuals I have met in my life. You've made my experiences at MIT unforgettable and I am proud to call many of you friends. I want to extend a sincere thank you to my friend ML, with whom we have discussed many topics in healthcare and constantly encouraged and helped one another.

Similarly, I would like to thank all my past and current mentors, colleagues and friends for your recommendations, guidance and friendship throughout the years. I would also like to thank my employer for supporting my educational and professional growth.

Last but most importantly special thanks go to my family.

To my sweetheart Lola - thank you for being my co-pilot. I am grateful for your love and patience throughout this journey.

To my sister Juni and my father Ilir – thank you for your love, kindness and your great sense of humor. You are the best sister and father a brother and son can wish for.

To my beloved mother Xheke (Jackie) – Above all, the most special thank you and this thesis dedication goes to you. Practically, all my achievements in life are without a doubt the result of your endless love, support and encouragement. Although not physically with us anymore, you are in our hearts and minds and continue to motivate us every day.

This page has been intentionally left blank

COVID-19 Therapeutics – A landscape analysis using systematic reviews and clinical data

by

Elvis Shehu

Submitted to the System Design and Management Program on February 19th, 2021 in Partial Fulfillment of the Requirements for the Degree of Master of Science in Engineering and Management

Abstract

2020 was a very unusual year due the COVID-19 pandemic that has caused many fatalities and is disrupting practically every aspect of our lives. It is unprecedented to see PubMed literature entries on a subject go from 0 to ~ 90,000 in a year. This effect is a direct result of the necessity of the scientific community to share data and insights generated worldwide. One of the potential unintended consequences of the sheer volume of literature in such a short amount of time is that many of it is not carefully peer-reviewed and vetted, making it difficult to sieve through information and understand it in order to allow informed decision making.

In this thesis, we conduct a critical evaluation of the scientific evidence and present the current landscape for COVID-19 therapeutics. We first discuss efforts to repurpose old drugs and to discover novel drugs against COVID-19. We then evaluate the clinical evidence of the most promising drug candidates that are approved or recommended for emergency use by relying on high quality systematic reviews as guided by the AMSTAR-2 tool and/or latest clinical evidence if no systematic reviews are available. Lastly, we discuss pressing challenges of the COVID-19 pandemic and provide conclusions and recommendations for future work.

Thesis Supervisor: Stan N. Finkelstein, MD
Title: Senior Research Scientist, IDSS

Disclaimer

The author is an employee of Sanofi. All views expressed in this thesis are solely those of the author and don't reflect or represent official positions of Sanofi company or any of its subsidiaries.

Thesis Organization

Chapter 1 provides an overview of the COVID-19 pandemic and its scientific and medical challenges. Here we introduce the motivation behind the thesis, its objective, and the approach undertaken to reach this objective.

Chapter 2 details the two different approaches to making drugs available for treatment, namely repurposing drugs already approved for other indications and developing new drugs specific for COVID-19. Starting from the biology of COVID-19 and its lifecycle, we discuss drug targets, mechanisms of action and the rationale for using repurposed vs. new therapeutics.

Chapter 3 summarizes the clinical evidence of the most promising candidate therapeutics that are approved or recommended for emergency use by relying on high quality systematic reviews as guided by the AMSTAR-2 tool and/or latest clinical evidence if no systematic reviews are available.

Chapter 4 discusses emerging challenges currently facing the scientific community with the new COVID-19 variants.

Chapter 5 summarizes conclusions.

Table of Contents

Table of Figures

Table of Tables

Abbreviations

$3CL^{pro}$	3C-like protease
ACE2	Angiotensin-converting enzyme 2
ACTIV	Accelerating COVID-19 Therapeutics Interventions and Vaccines
AI	Artificial Intelligence
AIDS	Acquired immunodeficiency syndrome
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
anti-GM-CSF	Anti-granulocyte-macrophage colony-stimulating factor
ARDS	Adult respiratory distress syndrome
BTK	Bruton's tyrosine kinase
CCR5	C-C Motif Chemokine Receptor 5
CD4	Cluster of Differentiation 4
CD6	Cluster of Differentiation 6
CD8	Cluster of Differentiation 8
China CDC	Chinese Center for Disease Control and Prevention
COVID-19	COronaVIrus Disease 2019
CRP	C-reactive protein
DHODH	Dihydroorotate dehydrogenase (DHODH)
EC50	Half maximal effective concentration
ECMO	Extracorporeal Membrane Oxygenation
EUA	Emergency Use Authorization
FDA	Food and Drug Administration

GM-CSF	Granulocyte-macrophage Colony-Stimulating Factor
GM-CSFR	Granulocyte-Macrophage Colony-Stimulating Factor Receptor
Hep C	Hepatitis C
HIV	Human immunodeficiency virus type
HIV-1	Human immunodeficiency virus type 1
IFN-γ	Interferon-gamma
IL-1	Interleukin 1
IL-10	Interleukin 10
IL-2	Interleukin 2
IL-23	Interleukin 23
IL-6	Interleukin 6
IL-8	Interleukin 8
JAK	Janus kinase
mAb	Monoclonal antibody
MCP-1	Monocyte chemoattractant protein-1
MERS	Middle East Respratory Syndrome
M^{pro}	Main protease
NIH	National Institutes of Health
NK	Natural killer
Nsps	Non-structural proteins
PD-1	Programmed cell death protein 1
PK/PD	Pharmacokinetics/pharmacodynamics

PL^{pro}	Papain-like protease
RBD	Receptor binding domain
RCT	Randomized control trial
RdRp	RNA-dependent RNA polymerase
RNA	Ribonucleic Acid
RSV	Respiratory syncytial virus
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	Severe Acute Respiratory Syndrome Corona Virus
SARS-CoV-2	Severe Acute Respiratory Syndrome Corona Virus 2
ssRNA	Single-stranded RNA
TMPRSS2	Transmembrane protease, serine 2
TNF	Tumor necrosis factor-alpha
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

1 Thesis Background

"The expert in anything was once a beginner." – Anonymous

With the vast amount of literature generated on COVID-19 in such a short period of time, there exists a potential for at best unintended misrepresentation of information to the wider community and at worst for disinformation and marketing of dubious treatments based on unsound scientific evidence trumpeted by snake oil salesman. Wikipedia misinformation dissemination examples on COVID-19 pandemic include ingesting miracle mineral solutions (i.e., industrial bleach), colloidal silver solutions among others to eradicate the virus. Indeed, a father and his sons were charged in Florida with marketing bleach as a "miracle" cure for COVID-19. With the goal of providing a science-based analysis of the efforts to develop therapeutics against COVID-19, this thesis reviews the evidence and progress made so far.

1.1 Overview of the COVID-19 pandemic

COVID-19 is a respiratory virus that has impacted the lives and livelihood of people all around the world. The virus was first detected in late December 2019, when Chinese local health authorities reported cases of patients with pneumonia of unknown cause, which were linked to a seafood and wet animal market in Wuhan, Hubei Province, China (1). After an epidemiologic and etiologic investigation performed by local health authorities in collaboration with the Chinese Center for Disease Control and Prevention (China CDC), the source of the pneumonia clusters was isolated and after sequencing, it was found to be a novel coronavirus named 2019-nCoV (2) which was later changed to SARS-CoV-2. This novel virus is structurally similar to the virus that causes severe acute respiratory syndrome (SARS) and poses major challenges for public health and medical communities, like SARS did in the first decade of 2000 and Middle East respiratory

syndrome (MERS) in the second decade (3). COVID-19 (COronaVIrus Disease 2019) is a highly infectious respiratory virus that is transmitted through air (4). Soon after its discovery in China, the virus quickly spread to countries all over the world and the World Health Organization (WHO) declared it a pandemic on March 11, 2020 (5). As of January 12, 2021, more than 90 million COVID-19 cases have been counted in over 190 countries, causing over 1.9 million deaths and counting (6). In the US, the number of total cases on January 12, 2021 was 23 million with over 384,000 deaths. The top 10 countries with the highest number of reported cases are the US, India, Brazil, Russia, UK, France, Turkey, Italy, Spain and Germany (Figure 1).

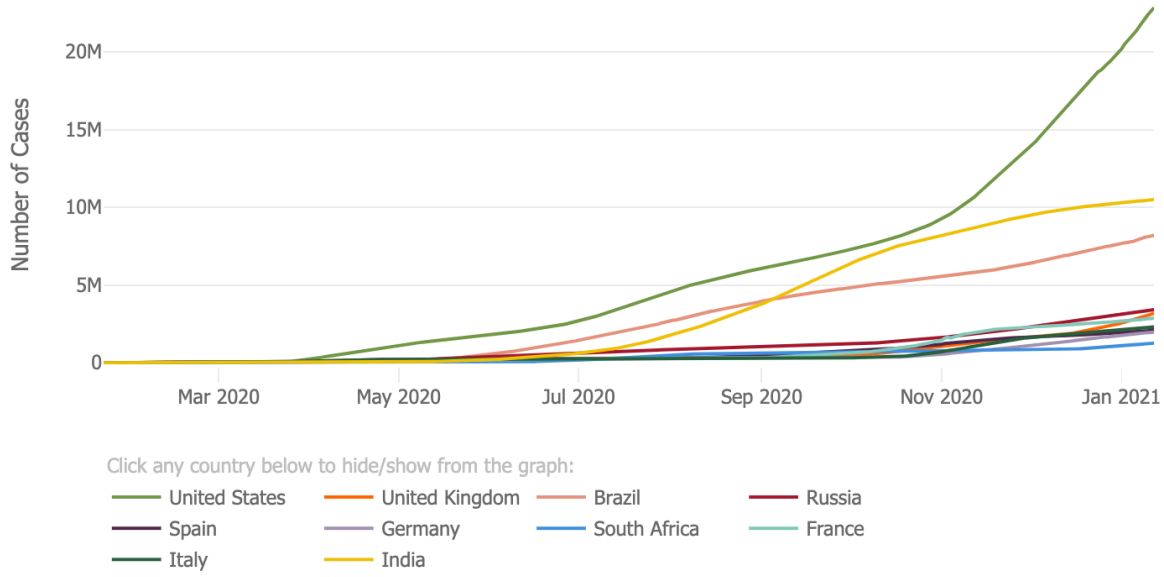

Figure 1: Number of cumulative cases by date for the top 10 countries with the highest number of infected patients (6).

With an average global mortality rate of 2% (7) , SARS-CoV-2 is ~14 times more deadly than the common flu (8). From a systematic review by He et al. which conducted a meta-analysis of 50,155 COVID-19 patients, 15.6% of patients were asymptomatic, 48.9% started asymptomatic and developed symptoms later, whereas the rest were symptomatic shortly after contraction of the

virus (9). From a study by Grant et al. where they evaluated data on 24,410 symptomatic patients (10), some of the clinical manifestations were fever (78%), cough (57%), and fatigue (31%). Out of the total patient population, 17% required non-invasive ventilation, 19% were admitted to an intensive care unit, 9% required invasive ventilation, 2% required extra-corporeal membrane oxygenation, and 7% died. Out of the hospitalized patients, mortality ranges between 15% and 20%, whereas out of patients requiring intensive care, it exceeds 40% (11). While it is worse than the flu in every metric, compared to other respiratory coronaviruses, such as SARS-CoV and MERS, SARS-CoV-2 has a higher transmission rate but lower mortality (12).

1.2 Motivation and Approach

As of the inception of this project, the goal has been to evaluate available treatments to date on COVID-19 from a scientific perspective, and to provide a summary of potential therapeutics tested in various stages of the disease progression along the patient's journey. Given the vast array of misleading information in the news leading to hydroxychloroquine being approved in the US for emergency use by the Food and Drug Administration (FDA) to then later being rescinded, it was particularly important to sieve through the scientific evidence and attempt to provide an unbiased picture of the viable treatment options investigated to date. However, with every passing day, the literature was being filled with a vast number of articles reviewing the multitude of treatment options being tried in clinical studies. Reading through this literature, it was becoming apparent that the conclusions in one article often conflicted with another, thus making it challenging to properly evaluate what information to trust and whether a particular treatment was effective or not. This led me to search for mechanisms to find trustworthy articles and eliminate bias in my literature search. I focused my analysis on articles that conduct systematic reviews

investigating the pools of clinical evidence. I used a validated tool developed to provide qualitative guidance in conducting systematic reviews in a thorough and unbiased way. AMSTAR (A MeaSurement Tool to Assess systematic Reviews) published in 2007 and updated in 2017 to AMSTAR-2 (13), is the standard tool used to evaluate the quality of the methodology used in systematic reviews. In this thesis, I will be employing AMSTAR-2 to sieve through all of the review articles that evaluate treatments related to COVID-19 and select the reliable articles in order to provide an evidence-based overview of treatments in the clinic and those approved by regulatory agencies in terms of their mechanism of action and effectiveness for treating the coronavirus. The reviews will be supplemented with clinical data and regulatory agency guidelines to further validate the findings or in the case where systematic reviews are not acceptable/available, they will be used as the main source of evidence.

1.3 Thesis Objective

The objective of this thesis is to provide the reader with a thorough analysis of therapeutics for COVID-19 and treatment landscape as of January 2021. The problem statement is as follows: **To** present a COVID-19 therapeutics landscape **by** critically and systematically assessing the scientific evidence conducted thus far **using** high quality systematic reviews complemented by clinical data from the literature.

2 Rationale for development of therapeutics for COVID-19

"Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less." – Marie Curie

Beyond public health measures to prevent transmission and infection, therapeutics are being investigated to help treat infected patients and their symptoms. According to clinicaltrials.gov, there are more than 500 potential therapeutic candidates being tested in thousands of clinical trials around the world. Efforts are also ongoing on discovery and pre-clinical testing with hundreds of candidates in the pipeline and the total numbers continue to grow (14). Clinical trials to date show that majority of trials are conducted with current marketed or late stage development drugs aiming to be repurposed for the treatment of COVID-19 (15). Repurposing drugs is highly advantageous as one can demonstrate more quickly whether they are successful in treating COVID-19 (16), resulting in faster delivery to patients. Hence, the large percentage of trials for repurposing drugs relative to new drugs is indicative of this interest. Nonetheless, new drugs should not be excluded as potential for treatment given that, as will be demonstrated in later sections of this thesis, none of the repurposed drugs approved to date are a cure for COVID-19. Figure 2 shows the typical pathway of the drug development process before it can be administered to patients for treatment of the desired indication.

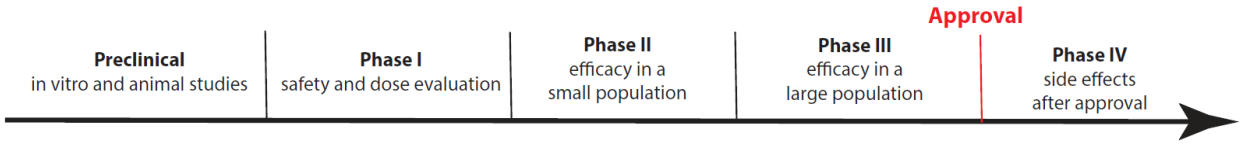

Figure 2: Typical drug development pathway

Although Figure 2 represents a simplified linear model, drug development is nothing but that. It is indeed a very complex and expensive system with a high failure rate (17). The rate limiting step to bringing a new drug to market is the trial-and-error based approach to the drug development process. For example, one can design a drug compound, but its pharmacokinetics/pharmacodynamics (PK/PD) properties may not be desirable or it may not be possible for it to be formulated into an oral tablet/capsule such that it is stable for a useful period of time. For the latter case, once the formulation stability issue is noted, a different formulation needs to be developed until a stable formulation is found. Similarly, during phase I clinical trials it may be observed that one of the ingredients (active or inactive) in the drug tablet is in a large dose that it generates undesired toxicity to patients. This observation would require the drug developer to go back to the lab to reduce the quantity of that ingredient. Additionally, in phase II/III clinical trials the active pharmaceutical ingredient may not be effective in treating COVID-19, which would bring the project to a halt and force the team of scientists to start from scratch. While the examples given are rather basic, they aim to offer a taste of how complex and resource intensive this system is, such that developing a new drug can almost inevitably take several years before it can be marketed and made available for patient use. To shorten this timeline, it is advantageous to repurpose drugs that are already marketed or in later stages of clinical trials, since there is already prior knowledge with regards to their PK/PD profiles, their safety and efficacy already gathered during the process to seek approval in the original indication. For example, previously approved antivirals could be effective against COVID-19. But, in order to identify and repurpose drugs that would be relevant in treating COVID-19, it is important to first understand the virus lifecycle (section 2.1), key biological steps, and target proteins to allow evaluation of

whether existing drugs have the potential to disrupt the virus lifecycle (section 2.2). While developing new therapeutics is a highly risky endeavor with low probability of success, the unprecedented nature of this pandemic has created the need to explore new therapeutics in addition to the repurposing efforts of current therapeutics in spite of the aforementioned bottlenecks. The new therapeutics are discussed in section 2.3.

2.1 Virus Biology

According to the Baltimore Classification system, SARS-CoV-2 is a class IV, positive-sense single-stranded RNA (ssRNA) virus that belongs to the β-lineage of the coronaviruses, which also includes SARS-CoV and MERS-CoV. DNA sequencing and alignment showed that the closest match of the SARS-CoV-2 virus was a bat SARS-like strain, BatCov RaTG13, at 96% match, suggesting a potential bat origin for SARS-CoV. Furthermore, sequence analysis showed that SARS-CoV-2 and SARS-CoV were ~79% similar at the nucleotide level. However, the spike (S) protein, the key surface protein involved in host cell entry, shares only ~72% similarity between the two SARS-CoV viruses (18–21). Coronaviruses have large genomes with sizes ranging from 26 to 32 kilobases (kb) with SARS-CoV-2 having a genome size of ~30kb (19). Like SARS CoV, SARS-CoV-2 is made up of two large polyproteins: ORF1a and ORF1ab (which encode the pp1a and pp1ab proteins and which form 16 nonstructural proteins (nsps) after getting cleaved), four structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) (Figure 3), and eight accessory proteins (22). Among the structural and non-structural proteins, the spike protein, membrane protein, envelope protein, nucleocapsid protein, 3CL protease ($3CL^{pro}$ or M^{pro}), papain like protease (PL^{pro}), RNA polymerase (RdRp), and helicase protein can be potential antiviral drug targets (22). The spike (S) glycoprotein, a key transmembrane protein ~ 150 kDa located in the

outer portion of the virus, facilitates binding to the host cells by interaction with the angiotensin-converting enzyme 2 (ACE2) expressed in lower respiratory tract cells.

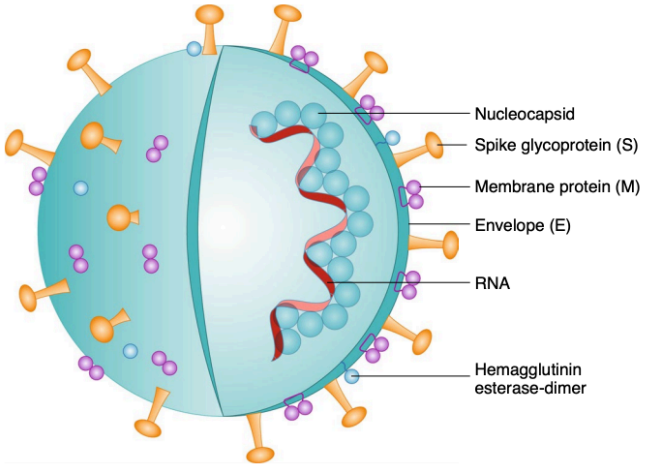

Figure 3: Schematic representation of the COVID-19 virus structure (23)

2.2 Repurposed COVID-19 Drugs and their Proposed Mechanisms of Action

Overall, we have grouped the drugs that are being tested/repurposed into three groups, those early in the lifecycle focused on inhibiting the virus entry (section 2.2.1), those that inhibit virus replication following entry of the viral load inside the host cell (section 2.2.2), and those later in the virus lifecycle which focus more towards managing the symptoms as the disease progresses (section 2.2.3). In each section we describe the mechanisms of action of each repurposed drug and any preclinical evidence of effectiveness against SARS-CoV-2 infection.

2.2.1 Virus Entry Inhibitors

The first step in the COVID-19 virus lifecycle is entry into the cell which is mediated by the spike S protein. The S protein has two domains. Domain S1 recognizes the angiotensin-converting enzyme 2 (ACE2) receptor, while domain S2 is involved in membrane fusion allowing the virus to deliver its cargo into the host cells (24) (Figure 4A).

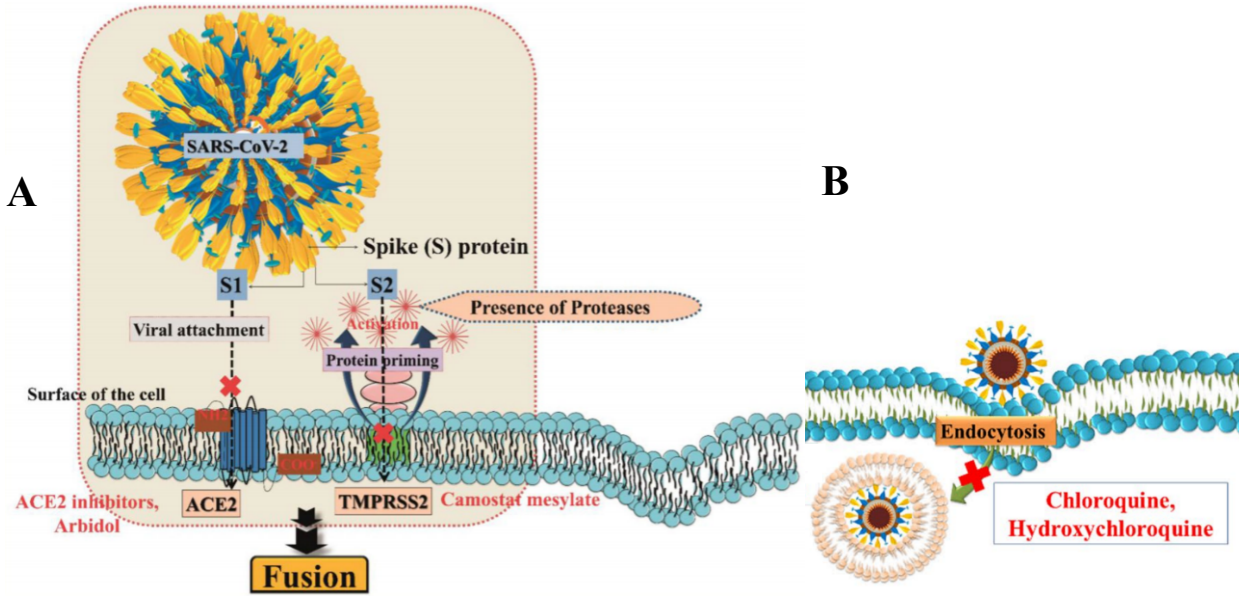

Figure 4: Mechanisms of SARS-CoV-2 entry into the human host cell by A) Receptor-mediated fusion, B) Endocytosis. Adapted from (25)

As the first step in the infection process, inhibiting the virus from entering the cell is an attractive proposition, which has also been used to develop drugs for other viruses such as human immunodeficiency virus type 1 (HIV-1) and Ebola (26)(27). Many peptide analogs, monoclonal antibodies (mAbs) and small molecules have been and/or are being tested *in vitro* to determine whether they inhibit the SARS-CoV-2 virus entry. For example, chloroquine, a small molecule used for malaria and amoebiasis treatment, was shown to be effective in inhibiting the SARS-CoV-2 virus *in vitro* (28). As a membrane fusion inhibitor, chloroquine increases the endosomal pH required for the fusion of the virus with cell and also may impair the terminal glycosylation of the cellular ACE2 receptor, therefore lowering the affinity of SARS-CoV-2 to ACE2 (24). Hydroxychloroquine, an analog of chloroquine, with a similar mechanism of action as chloroquine but with less toxicity, has also been found effective in inhibiting SARS-CoV-2 infection *in vitro* (29). In addition to virus-host cell binding via the ACE2 receptor, the proteolytic cleavage of coronavirus S proteins by host cell-derived proteases is required. Transmembrane protease, serine

2 (TMPRSS2) and furin are both essential proteases that are required for the activation of SARS-CoV-2 in human airway cells (Figure 4). *In vitro* data have demonstrated that inhibition of either TMPRSS2 or furin can negatively affect the ability of SARS-CoV-2 to mediate virus entry and membrane fusion (30). Inhibition of TMPRSS2 has been shown sufficient to prevent SARS-CoV-2 entry in lung cells in an *in vitro* setting (31). Evaluation of two TMPRSS2 inhibitors, nafamostat mesylate and camostat mesylate, in clinical trials is supported by *in vitro* studies that have established their antiviral activity against the SARS-CoV-2 virus (32). *In vitro* data has also shown that combination of TMPRSS2 and furin inhibitors can act synergistically to inhibit SARS-CoV-2 activation and multiplication at lower doses than either protease inhibitor alone (30). The aforementioned drugs are only a subset of drugs that targeting viral entry. A list of drugs that target viral entry and that have undergone and/or are currently undergoing clinical trials for COVID-19 repurposing purposes is shown in Table 1. In this table we also report corresponding evidence of drug effectiveness in various cell lines *in vitro* and in animals. In absence of *in vitro* and animal studies, we report other potential evidence e.g., *in silico*.

Table 1: List of drugs targeting viral entry

Drugs	**Current Indication**	**Mechanism of Action**	**Preclinical evidence**
Chloroquine (Aralen)	Malaria	Membrane Fusion Inhibitor, Endocytosis	At low doses, it potently blocked SARS-CoV-2 infection in Vero E6 cells (28) In mice, it significantly reduced lung inflammation but it did not diminish viral replication (33)
Hydroxychloroquine (Plaquenil)	Malaria	Membrane Fusion Inhibitor, Endocytosis	At moderate doses, it effectively inhibited the entry step and post-entry

			stages of SARS-CoV-2 in Vero E6 cells (29) At clinically relevant doses, it did not significantly inhibit SARS-CoV-2 infection in human respiratory tissue model of primary nasal and bronchial cells (33) In hamsters, it had insignificant reductions of virus titer in the lungs (33)
Artemisinin (Coartem)	Malaria	Unknown	At very high doses it inhibited the SARS-CoV-2 infection of Vero E6 cells (34)
Nafamostat mesylate (Fusan)	Pancreatitis	Serine protease TMPRSS2 inhibitor	At moderate doses, it inhibited SARS-CoV-2 infection in Vero E6 cells (28) At low doses, it inhibited SARS-CoV-2 entry into human lung cells (35)
Camostat mesylate (Foipan)	Pancreatitis	Serine protease TMPRSS2 inhibitor	It partially blocked entry of SARS-CoV-2 into Caco-2 and Vero E6 cells (31)
Maraviroc* (Selzentry)	HIV	Virus entry inhibitor	At moderate doses it did not reduce SARS-CoV-2 infection on Vero E6/TMPRSS2 cells (36)
Umifenovir (Arbidol)	Influenza	Membrane Fusion Inhibitor	At moderate doses, it inhibited SARS-CoV-2 infection in Vero E6 cells (37)
Telmisartan** (Micardis)	Cardiovascular	ACE2 inhibitor	Even at high doses, it did not inhibit SARS-CoV-2 infection in primary cells (38)
Valsartan** (Diovan)	Heart failure; hypertension	Angiotensin Receptor Blocker	Through structure-based virtual screening, it was predicted as a potential

			inhibitor of SARS-CoV-2 M^{pro} main protease (39)
Losartan** (Cozaar)	Diabetic nephropathy	Angiotensin Receptor Blocker	At moderate to high doses, it reduced SARS-CoV-2 replication in Vero E6 cells (40)
Colchicine** (Colcrys)	Gout	ACE2 inhibitor	At high doses, it inhibited SARS-CoV-2 infection in primary cells (38)

*Maraviroc has a dual function. It serves as an entry inhibitor and potential viral protease inhibitor (Table 2) based on *in silico* data (41)
**These drugs have multiple mechanisms of action and their mechanism of inhibiting SARS-CoV-2 infection is not known.

It is noteworthy that for some drugs the preclinical evidence does not support further testing in clinical trials. For example, artemisinin had an effect at a very high dose, which probably won't be achievable at clinically relevant doses. Similarly, maraviroc showed no effect at inhibiting SARS-CoV-2 in Vero E6/TMPRSS2 cells. Yet, it is being pursued in clinical trials (NCT04435522). It is unclear whether the preclinical evidence requirement was waived due to the urgency of the situation or whether it wasn't needed due to the fact that these drugs are already approved for other indications, and as such their mechanisms of action and safety profiles are already known. Hydroxychloroquine is an interesting case as there is both positive and negative preclinical evidence of its effect. However, the positive preclinical evidence was published in March whereas the negative evidence in August. Hence, one could argue that at the time of initiation of clinical trials, the positive results were sufficient to justify further testing.

2.2.2 Virus Translation, Replication, and Assembly Inhibitors

After the virus entry into the host cells, the next step is the translation of the replicase gene which encodes 2 large polyproteins pp1a and pp1ab (Figure 5). These 2 polyproteins contain the non-structural proteins (nsps) 1-11 and 1-16, which get cleaved into the individual nsps by

proteases. Many of these nsps assemble into the replicase–transcriptase complex (42). Some nsps are key potential drug targets. For example, nsp3 and nsp5 are proteinases, with nsp3 being PL^{pro} and nsp5 being $3CL^{pro}$ or M^{pro}. Nsp12 is RNA-dependent RNA polymerase (RdRp) and is a key protein in the replication of the viral RNA. Nsp13 is a helicase.

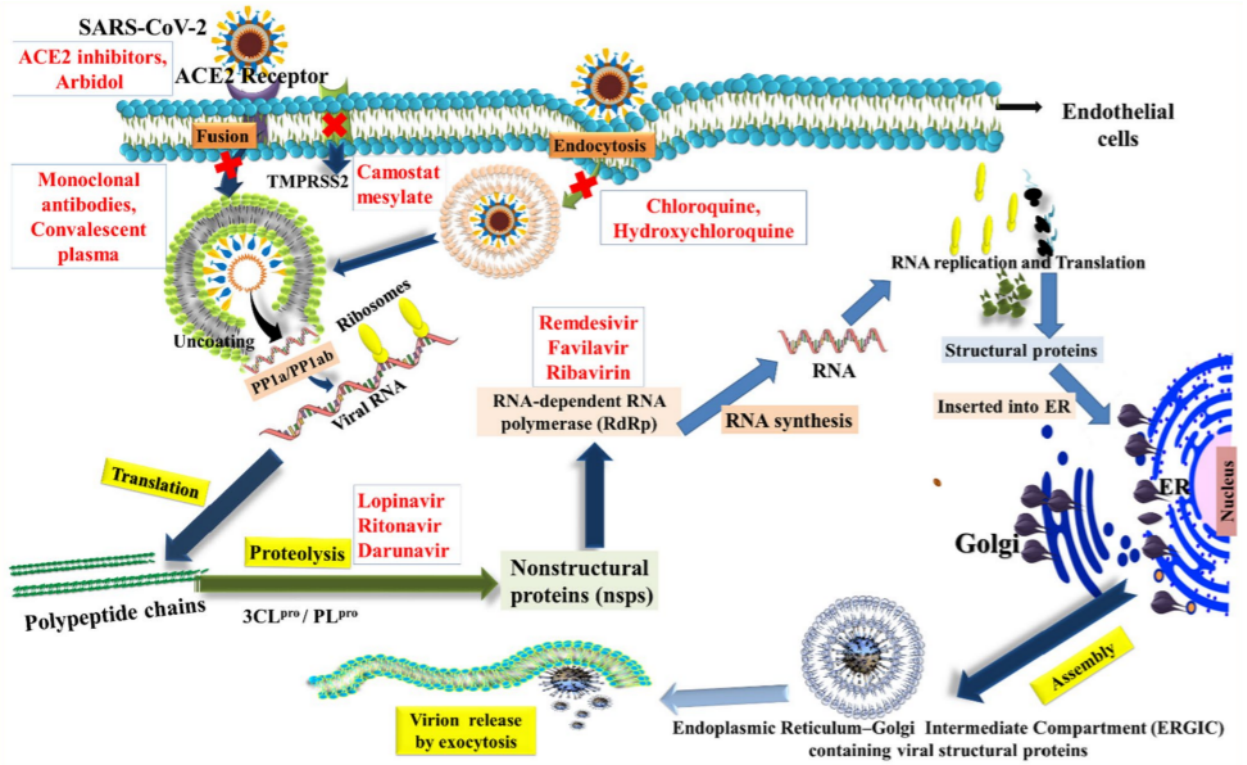

Figure 5: Schematic representation of the lifecycle of SARS-CoV-2 including some of the main targets of some of the drug therapies (25).

There are many protease and replication inhibitors that are being repurposed against COVID-19. Perhaps, the most well-known example of a RdRp inhibitor drug that is being repurposed against SARS-CoV-2 is remdesivir. Remdesivir is a nucleotide analogue prodrug that was initially evaluated in a clinical trial against the Ebola outbreak in the Democratic Republic of the Congo in 2014, but its testing was terminated after an interim analysis found it inferior to 2 other antibody therapeutics with regards to mortality (43,44). Recent studies have shown remdesivir to inhibit the

replication of SARS-CoV-2 virus *in vitro* as well as *in vivo* in mice (28,45). There are also several protease inhibitors currently used to treat human immunodeficiency virus (HIV) such as lopinavir, ritonavir, darunavir, atazanavir, that have been proposed as potential treatments to inhibit the translation process of SARS-CoV-2 RNA. Lopinavir and ritonavir are viral protease inhibitors targeting the $3CL^{pro}$ protein. One study has shown that they inhibit the replication of SARS-CoV-2 *in vitro* (46) while another has shown that lopinavir is not an effective protease inhibitor for SARS-CoV-2 (47). On the other hand, although darunavir did not show any antiviral activity against SARS-CoV-2 *in vitro* (48) study, it is still being pursued in clinical trials due to anecdotal evidence (49).

Towards the end of the virus lifecycle, structural proteins are synthesized, which in turn lead to assembly and release of viral particles (Figure 5). There are some drugs in the last steps of the virus lifecycle prior to exocytosis that have also been investigated *in vitro* against SARS-CoV-2 but, similar to some drugs in section 2.2.1, the results have not been supportive of testing in clinical trials (e.g., oseltamivir (50)). A list of drugs in clinical trials that target the virus translation, replication and assembly steps is shown in Table 2.

Table 2: List of drugs targeting viral translation, replication and assembly

Drugs	**Current Indication**	**Mechanism of Action**	**Preclinical evidence**
Remdesivir (Veklury)	Ebola	RdRp inhibitor	At low doses, it potently blocked SARS-CoV-2 infection in Vero E6 cells, human lung cells and primary human airway epithelial cultures (28)(45)
Favipiravir (Avigan)	Influenza	RdRp inhibitor	At high doses, it reduced SARS-CoV-2 infection in Vero E6 cells (28) At high doses, it

			significantly reduced SARS-CoV-2 titers in the lungs of hamsters (51)
Glecaprevir	Hepatitis C	Viral protease inhibitor	Through structure-based virtual screening, it was determined as a potent inhibitor of SARS-CoV-2 M^{pro} receptor (41)
Maraviroc* (Selzentry)	HIV	Viral protease inhibitor (based on in silico study (41))	Through structure-based virtual screening, it was determined as a potent inhibitor of SARS-CoV-2 M^{pro} receptor (41)
Emtricitabine/tenofovir (Emtriva/Viread)	AIDS	Reverse transcriptase inhibitor	In ferrets it showed no effect in reducing viral titer compared to placebo over the course of 14 days, except on day 8 (52)
Sofosbuvir (Sovaldi)	Hepatitis C	Virus replication inhibitor	In silico, it showed to bind tightly to RdRp receptor (53)
Atazanavir (Reyataz)	Hepatitis C	Viral protease inhibitor	At moderate doses, it inhibited SARS-CoV-2 replication in Vero E6 cells, in human pulmonary epithelial cells, and in primary human monocytes (54)
Daclatasvir (Daklinza)	Hepatitis C	Virus replication inhibitor	At low and moderate doses, it inhibited the production of infectious SARS-CoV-2 virus particles in Vero E6, HuH-7, and Calu-3 cells (55)
Ivermectin (Stromectol)	Parasitic infection	Nuclear transport inhibitor	At moderate doses, it reduced the quantity of SARS-CoV-2 virus in Vero cells (56)
Aprepitant (Emend)	Nausea and vomiting	Virus replication inhibitor	Through structure-based virtual screening, it was predicted as a potential

			inhibitor of SARS-CoV-2 Nsp13 helicase and M^{pro} receptor (57)(58)
Ribavirin (Rebetol)	Hepatitis C	Nucleic acid inhibitor	At high doses, it reduced SARS-CoV-2 infection in Vero E6 cells (28)
Niclosamide (Niclocide)	Viral infection	Virus replication inhibitor	At low doses, it reduced SARS-CoV-2 infection in Vero E6 cells (59)
Lopinavir (Kaletra)	AIDS	Viral protease inhibitor	At moderate doses, it reduced SARS-CoV-2 infection in Vero E6 cells (46)
Ritonavir (Norvir)	HIV/AIDS	Viral protease inhibitor	It showed no antiviral activity against SARS-CoV-2 in Vero E6 cells (46)
Darunavir/ Cobicistat Prezista/Tybost	HIV/AIDS	Protease inhibitor	It showed no antiviral activity against SARS-CoV-2 in Vero E6 cells (48)
Oseltamivir (Tamiflu)	Influenza	Neuraminidase enzyme inhibitor	It showed no antiviral activity against SARS-CoV-2 in Vero E6 cells (50)
Penciclovir (Denavir)	Herpes	Viral replication inhibitor	At high doses, it reduced SARS-CoV-2 infection in Vero E6 cells (28)
Nitazoxanide (Alinia)	Antiprotozoal	Viral protein expression inhibitor	At low doses, it inhibited SARS-CoV-2 infection in Vero E6 cells (28)
EIDD-2801 (molnupiravir or MK-4482)	Not approved yet	Virus Replication Inhibitor	It inhibited SARS-CoV-2 replication in immune deficient mice implanted with authentic human lung tissue (60)

*Maraviroc has a dual function. It serves as a virus entry inhibitor (Table 1) and potential viral protease inhibitor based on *in silico* data (41)

Similar to the observations in Table 1, some of the drugs reported in Table 2 do not have strong preclinical evidence to support human trials. For example, some drugs have been shown to be potentially effective inhibitors of various enzymes/receptors based on *in silico* studies but have not been tested in *in vitro* or in animals (e.g., sofosbuvir, aprepitant). Similarly, there are some drugs for which *in vitro* or animal data show no effect in reducing SARS-CoV-2 infection (e.g., oseltamivir, darunavir), yet they have or are being tested in human trials (NCT04516915, NCT04252274). Lastly, when high doses are needed to show an effect *in vitro*, it is an indication that the drug is likely to be ineffective in human trials (e.g., ribavirin) considering that such doses cannot be mimicked in patients under clinically relevant conditions. Thus, under normal circumstances, these drugs are not pursued further. Yet, ribavirin was pursued in clinical trials and was concluded to have no effect in reducing the infection in COVID-19 patients (61)(62). During our literature search, a noticeable trend was the proliferation of pre-print articles prior to being peer reviewed and published in scientific journals, presumably in the interest of distributing information quickly. Many of these articles have eventually been published in peer review journals while some have not and may even have gotten rejected. For example, the preclinical evidence on daclatasvir noted in Table 2 is from a pre-print publication and no corresponding peer-reviewed journal could be found. Thus, the information on daclatasvir may not be strong enough to justify progression into clinical studies. Yet, it is being tested in a Phase 2/3 clinical trial (NCT04443725). These examples suggest that a systematic approach in decisions on which drugs to investigate in clinical trials and which not to was lacking. The most prominent example is that of hydroxychloroquine. With regards to hydroxychloroquine, the decision to test in humans was

supported by an *in vitro* study by Liu et al. which showed efficacy of the compound in non-human cells (63). Yet, later *in vitro* and animal studies reported no efficacy of the compound (33).

In addition to the obvious cases in Table 1 and Table 2, where clinical trials are not justified (e.g., ribavirin, oseltamivir, maraviroc), it is notable that for some drugs, the preclinical evidence is contradictory depending on the article (e.g., hydroxychloroquine). This outcome has been in part due to a lack of standardized *in vitro* assays to test promising candidates against SARS-CoV-2. For example, different assays are done under different testing conditions using different cell lines. Similarly, a positive control is often not included. In efforts to rationally make decisions on whether to pursue human testing, standardizing *in vitro* tests are imperative. Similarly, decisions need to be made on which animal models are more representative of human conditions when testing COVID-19 therapeutics. This bottleneck contributed in part to the decision to form the Accelerating COVID-19 Therapeutics Interventions and Vaccines (ACTIV) public-private partnership in 2020 (63). ACTIV has four working groups: Preclinical Working Group, Therapeutics Clinical Working Group, Clinical Trial Capacity Working Group, and Vaccines Working Group. The preclinical working group is tasked with streamlining the preclinical evidence to better inform decisions of going into clinical trials and with prioritizing compounds for limited preclinical and clinical resources.

2.2.3 Symptoms Management Inhibitors (immunomodulatory and others)

While symptoms following COVID-19 infections vary from asymptomatic to mild to severe, a common issue for symptomatic patients is the upregulation of immune response and systemic inflammation. In a subset of patients, particularly in patients with comorbidities, the aberrant immune response can lead to severe acute lung injury in the form of adult respiratory distress

syndrome (ARDS), which may progress to multiorgan injury and failure. Recent research in COVID-19 patients has implicated many elevated inflammatory biomarkers, cytokines and chemokines, with very high levels in those patients that have the most severe form of the disease (64)(65). Some examples include interleukins (IL-1, IL-2, IL-6, IL-8, and IL-10), tumor necrosis factor-alpha (TNF), interferon-gamma (IFN-γ), granulocyte-macrophage colony stimulating factor (GM-CSF), monocyte chemoattractant protein-1 (MCP-1) and C-reactive protein (CRP). Furthermore, there is a significant reduction in the CD8+ and CD4+ T cells, as well as natural killer (NK) immune cell populations (64)(65) (Figure 6). Hence, the rationale to use drugs which can tame the uncontrolled inflammation and immune response is justified.

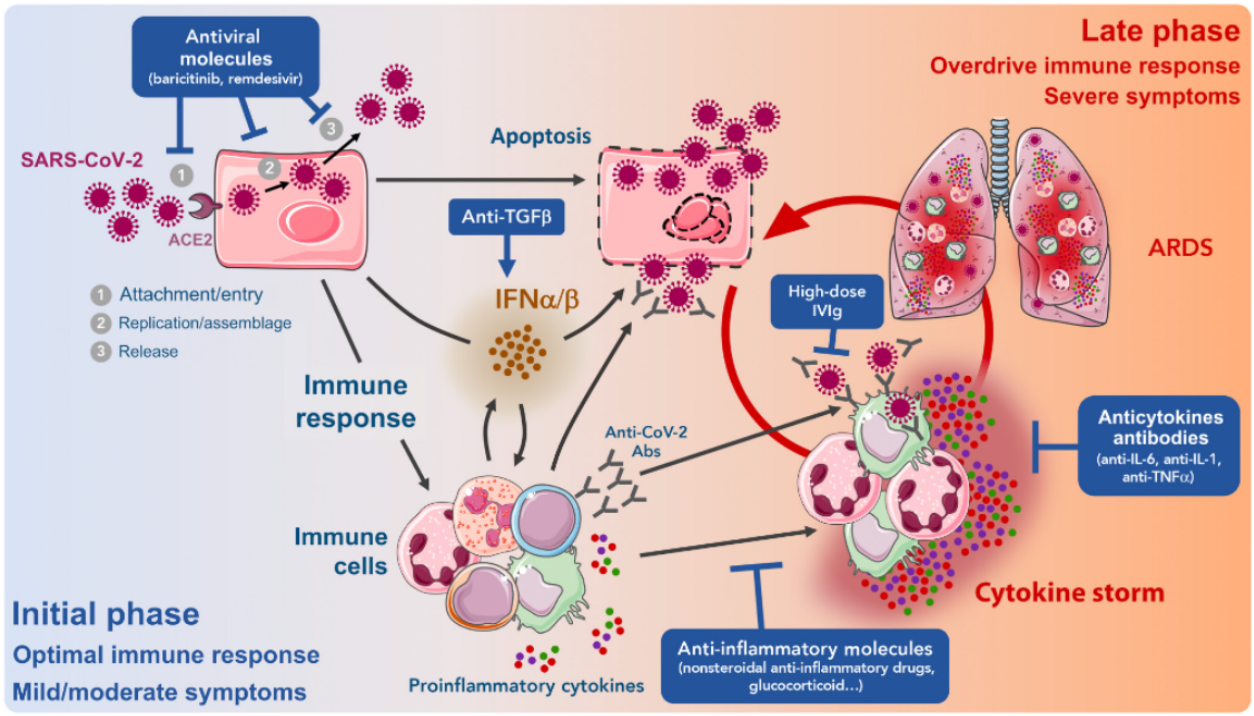

Figure 6: Mechanism of COVID-19 lifecycle and inflammatory response (66).

Some examples that are being tested include Il-6 inhibitors tocilizumab, sarilumab, and siltuximab, IL-1 inhibitor anakinra, janus kinase (JAK) inhibitors such as baricitinib and

ruxolitinib, corticosteroids such as dexamethasone, interferon beta-1a and 1b, TNF inhibitors, anti-GM-CSF antibody mavrilimumab, anti CD6 mAb itolizumab etc. Table 3 shows a list of immunomodulatory drugs and signaling agents that are being tested in clinical trials against COVID-19.

Table 3: List of therapeutics being evaluated in clinical trials for the management of symptoms related to COVID-19

Drugs	**Approved for**	**Mechanism of Action**	**Preclinical evidence**
Tocilizumab (Actemra)	Rheumatoid arthritis	IL-6R inhibitor	N/A
Sarilumab (Kevzara)	Rheumatoid arthritis	IL-6R inhibitor	N/A
Siltuximab (Sylvant)	Idiopathic multicentric Castleman disease	IL-6 inhibitor	N/A
Clazakizumab	Not approved yet	IL-6 inhibitor	N/A
Sirukumab	Not approved yet	IL-6 inhibitor	N/A
Baricitinib (Olumiant)	Influenza	JAK inhibitor	It resolved lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques (67)
Ruxolitinib (Jakafi)	Steroid-Refractory Acute Graft-Versus-Host Disease	JAK inhibitor	N/A
Mavrilimumab	Not approved yet	GM-CSFRα inhibitor	N/A
Lenzilumab	Not approved yet	GM-CSFR inhibitor	N/A
Gimsilumab	Not approved yet	GM-CSFR inhibitor	N/A
Leronlimab	Not approved yet	CCR5 co-receptor blocker	N/A
Azithromycin (Zithromax)	Bacterial infections	Ribosomal subunit inhibitor	At low doses, it had antiviral activity against SARS-CoV-2 in Vero E6 cells (59)
Camrelizumab (AiRuiKa)	Hodgkin lymphoma	PD-1 inhibitor	N/A
Eculizumab (Soliris)	Atypical hemolytic uremic syndrome,	Terminal complement protein C5 inhibitor	N/A

	paroxysmal nocturnal hemoglobinuria		
Bevacizumab (Avastin)	Multiple cancers, eye disease	VEGF inhibitor	N/A
Itolizumab (Alzumab)	chronic plaque, psoriasis (India)	CD-6 inhibitor	N/A
Corticosteroids (dexamethasone, hydrocortisone etc.)	Inflammation	Several mechanisms	N/A
Interferons (interferon-beta 1a, 1b etc.)	Inflammation	Several mechanisms	N/A
Anticoagulants (heparin)	Venous thrombosis	Antithrombin III activator	N/A
Canakinumab (Ilaris)	Cryopyrin-Associated Periodic Syndrome	IL-1 inhibitor	N/A
Anakinra (Kineret)	Rheumatoid Arthritis, Cryopyrin-Associated Periodic Syndrome	IL-1 inhibitor	N/A
IMU-838 (vidofludimus calcium)	Not approved yet	Dihydroorotate dehydrogenase (DHODH) inhibitor	At moderate doses, it showed SARS-CoV-2 anti-viral effect in Vero E6 cells (68)
Acalabrutinib (Calauence)	chronic lymphocytic leukemia, small lymphocytic lymphoma	Bruton's tyrosine kinase (BTK) inhibitor	N/A
Risankizumab (Skyrizi)	Psoriasis	anti-IL-23 antibody	N/A
Adalimumab (Humira)	Rheumatoid arthritis	Tumor necrosis factor (TNF) inhibitor	N/A

N/A = not available

There is no specific preclinical evidence in relevant models to support some of these agents (specified as N/A in Table 3). Most of the rationale is based on previous indirect evidence (e.g., IL-6) or on findings that have shown an increase of many of such immunomodulatory or signaling pathways agents retrospectively from patient samples and some clinical subgroup analysis when

such agents are used off-label. For example, evidence for a potential beneficial role of canakinumab, an IL-1 inhibitor is supported by a retrospective subgroup analysis (69). It is also important to note that while immunomodulatory drugs are intended for late stages of disease, at the middle stages, some of them are administered alongside antivirals (section 2.2.2) to provide maximum effect (70).

2.3 Efforts in developing new therapeutics

In addition to attempts to repurpose known antiviral drugs, efforts are ongoing to discover and develop new therapeutics against key targets in the COVID-19 virus lifecycle. In this section, we describe some of these efforts. Specifically, we discuss various small molecules, peptides (section 2.3.1), and monoclonal antibodies (section 2.3.2) that are being investigated in preclinical and clinical studies to treat COVID-19 patients.

2.3.1 Discovery of small molecules and peptides

As described earlier in section 2.2.2, many repurposed drugs developed for HIV, Hepatitis C virus or Ebola target viral proteases. The main protease M^{pro} also known as $3CL^{pro}$ is a critical protease conserved among coronaviruses which lacks a human homolog, making it a promising and specific target for SARS-CoV-2 (71). In fact, M^{pro} was previously shown to be a validated target for drugs against SARS-CoV and MERS-CoV (72).

Based on the structural analysis of the M^{pro} protein, many groups have discovered lead compounds that block its function in various *in vitro* assays (47,73–76) and provide a starting point for further development of COVID-19 therapeutics. For example, Dai et al., after analyzing the structure of the M^{pro} active site, were able to design two inhibitors 11a and 11b, that strongly inhibit the activity of M^{pro} and show good antiviral activity in cell culture assays. 11b also showed good

pharmacokinetic parameters and low toxicity when tested in animals (73). Jin et al. were able to identify six compounds that inhibited M^{pro}, with half-maximal inhibitory concentrations ranging from 0.67 to 21.4 μM by combining structure-assisted drug design, virtual drug screening, and high-throughput screening. One of the six, ebselen, showed encouraging antiviral activity in cell-based assays (74). Similarly, by screening a library of protease inhibitors, Ma et al identified four compounds (boceprevir, GC-376, calpain inhibitors II and XII) that inhibit SARS-CoV-2 viral replication in cell culture with a half maximal effective concentration (EC50) ranging from 0.49 to 3.37 μM (47). Importantly, boceprevir and calpain inhibitors II and XII represent novel chemotypes. Brahman et al, carried out molecular docking studies on potential inhibitory action of novel azo imidazole derivatives against COVID-19 M^{pro} (77).

PL^{pro} is another conserved protease that can be a potential druggable target. Using a combinatorial library, Rut et al, found a SARS-CoV-2 PL^{pro} substrate site while peptide library screening identified two PL^{pro} specific inhibitors, VIR250 and VIR251 (78). Solving the crystal structure of the inhibitors with the PL^{pro} protease provides a foundation for the discovery of future potential therapeutics. No information is yet publicly available on any further testing of these two inhibitors *in vitro* or preclinical studies.

Various other approaches are also being used to find potential repurposed therapeutics using tools such as machine learning and mechanistic models of signal transduction circuits related to SARS-CoV-2 infection (79) as well as Artificial Intelligence (AI) (80). However, they are all in early stages and no target hits have been developed for further testing.

2.3.2 Discovery and development of monoclonal antibodies

Monoclonal antibodies are another category of drugs that are being developed against the SARS-CoV-2 virus. The majority of mAbs are neutralizing antibodies due to their ultimate function of neutralizing/dismantling the virus from cell attachment and entry. Neutralizing antibodies designed against the SARS-CoV-2 virus are helpful tools against COVID-19 with potential for both prophylactic and therapeutic effect. Developing antibodies against respiratory viruses is not new and they are used in the clinic prophylactically. For example, palivizumab is a monoclonal antibody approved for the prevention of respiratory syncytial virus (RSV) in children at high-risk for infection (81). There are currently many antibodies against COVID-19 progressing in the R&D pipeline with 66 in the discovery phase, 60 in the preclinical phase, and 79 in clinical trials (83). The majority of antibodies being developed are targeting the viral spike protein (S) of SARS-CoV-2, which as described previously, is a critical step in the viral attachment and entry to the host cell via the ACE2 receptor. Indeed 25 out of 79 antibodies in development are targeting the S protein. Additionally, all of the antibodies in Phase 3 testing target the S protein (Table 4).

Table 4: List of antibodies in Phase 3. Adapted from (82).

No.	Antibody	Company/Collaborator
1	Bamlanivimab (LY3819253, LY-CoV555)	AbCellera/Eli Lilly/NIH
2	REGN-COV2 (REGN10933/Casirivimab + REGN10987/Imdevimab)	Regeneron/NIAID
3	Sotrovimab (VIR-7831/GSK4182136)	Vir biotechnology/GSK
4	AZD7442 (AZD8895/Tixagevimab + AZD1061/Cilgavimab)	AstraZeneca/Vanderbilt University Medical Center/DARPA/BARDA
5	Regdanvimab (CT-P59)	Celltrion
6	TY027	Tychan
7	BRII-196 + BRII-198	Brii Biosciences/NIAID

Most of the anti-SARS-COV-2 antibodies are isolated from B cells derived from convalescent plasma of COVID-19 patients or immunized transgenic animals. Once isolated and identified, neutralizing antibodies can be engineered further in order to increase their half-life from weeks to months and produced in bulk for patient administration. Two antibodies in the clinic so far have demonstrated benefit in targeting the S protein and inhibiting viral entry and have as a result received Emergency Use Authorization (EUA) by the US FDA, specifically 1) bamlanivimab and 2) casirivimab plus imdevimab antibody cocktail.

Bamlanivimab, also known as LY-CoV555, is a neutralizing antibody with high-affinity binding to the RBD domain and ACE2 binding inhibition (83). It was originally identified using microfluidic high-throughput screening of antigen-specific B-cells derived from the convalescent plasma of a COVID-19 patient. This monoclonal antibody was shown to reduce the viral replication in the upper and lower respiratory tract in a non-human primate model of SARS-CoV-2 infection (83) and is currently being studied in human trials. It is important to note that as of February 2021 this preclinical evidence in non-human primates has not been peer reviewed. Clinical trial results have allowed bamlanivimab to receive an EUA from the US FDA and are discussed in detail in section (3.2.5.1).

As is typical with most viruses, spike protein mutations arise that are resistant to individual antibodies. Baum et. al showed that by employing an antibody cocktail strategy instead of one antibody, they were able to minimize mutational escape by SARS-CoV-2, especially using antibody cocktails in which the two antibodies bind to distinct and non-overlapping regions of the receptor binding domain (RBD) of the spike protein (84). In a follow up study, Baum et al, evaluated this cocktail of neutralizing antibodies, casirivimab (REGN10933) and imdevimab

(REGN10987) also known as REGN-COV-2, in rhesus macaques and hamsters and showed benefits in both animal models (85). The two antibodies act in unison, where the antigen-binding fragment of casirivimab binds at the top of RBD, overlapping almost completely with the binding site for ACE2, while imdevimab acts on the side of RBD diminishing the probability of the virus interfering with ACE2. When testing each antibody separately mutant viruses were generated, whereas in the presence of the REGN-COV-2 cocktail mutant viruses failed to be generated efficiently (84).

3 Therapeutics approved or recommended for emergency use

"There is divine beauty in learning. To learn means to accept the postulate that life did not begin at my birth. Others have been here before me, and I walk in their footsteps." ― Elie Wiesel

In this chapter we review the clinical evidence of the most promising candidate therapeutics that are approved or recommended by various regulatory bodies for emergency use based on randomized clinical trials (RCT). We rely on the evidence and conclusion of highly rated systematic reviews by using the AMSTAR-2 tool to provide as accurate and unbiased results as possible. For the most recently approved or recommended treatments, we have used the latest clinical evidence if no systematic reviews are available.

3.1 Methodology of Analysis of Systematic Reviews for COVID-19 Treatment

3.1.1 Database Search

We searched for systematic reviews and/or meta-analyses in four databases: PubMed, EMBASE, Cochrane, and Medline, by November 21, 2020. We used a combination of keywords and boolean expressions during the search. We included all systematic reviews which contained Covid 19, Sars Cov 2 or nCov and treatment or therapeutics and systematic review or meta-analysis in the title or abstract (Table 5). More detailed information on the search queries for each database and corresponding limits is available in the Appendix (section 6). We also performed similar database and Google searches for more recently developed therapeutics without systematic reviews.

Table 5 - Database Search Query

Term 1			**Term 2**			**Term 3**	
OR	COVID 19	AND	OR	Therapeutic	AND	OR	Systematic Review
	Sars Cov 2						
	Sars Cov2			Treatment			Meta analysis
	2019 nCoV						

3.1.2 Inclusion/Exclusion Framework

After removing duplicates, the following were excluded: (1) reviews where therapeutics were not the main point of the review, (2) reviews using *in vitro* or animal data, (3) non-systematic reviews, (4) protocols for anticipated systematic reviews, (5) non-English publications, and (6) where publication text was not found. A detailed analysis on included and excluded articles is shown in Figure 7.

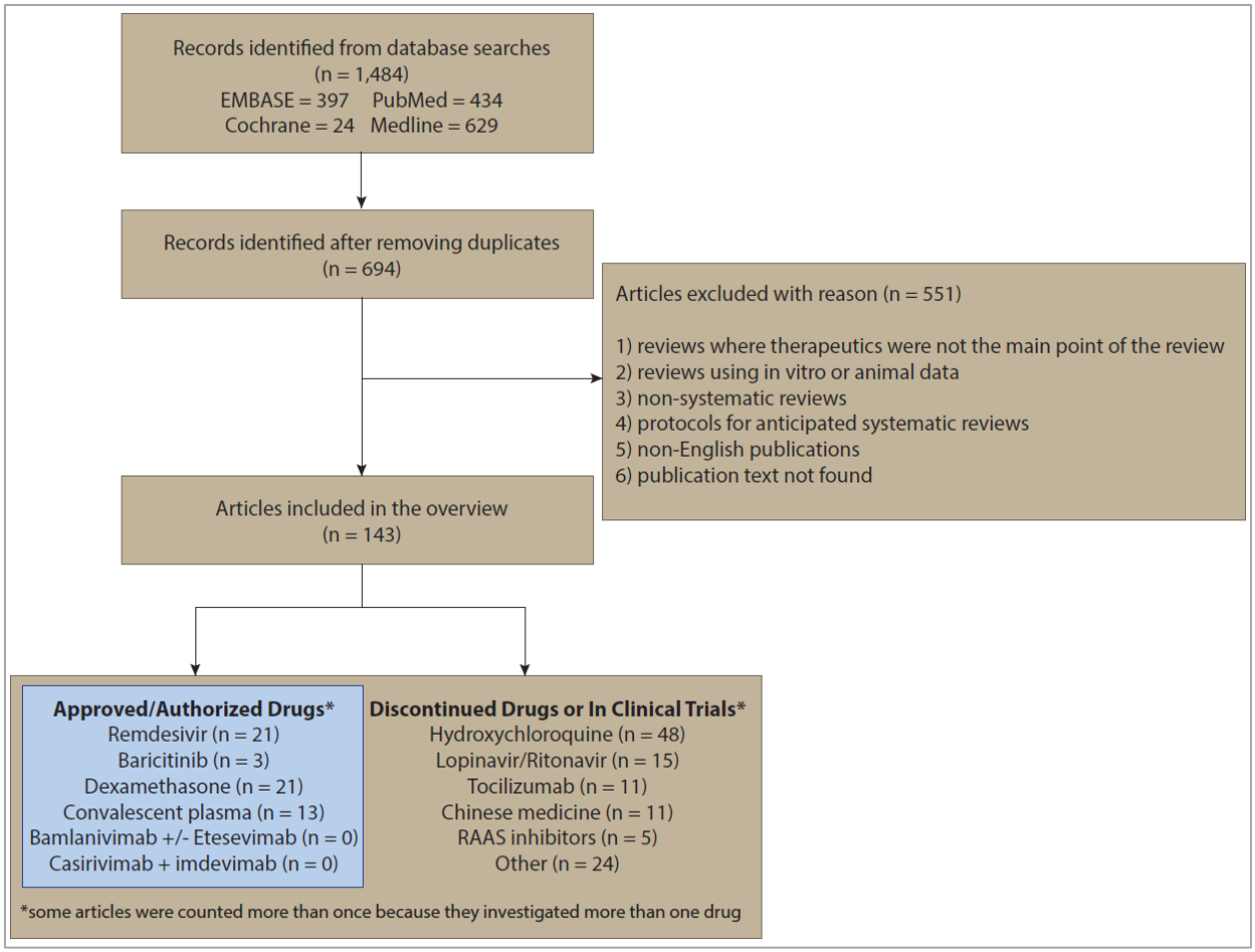

Figure 7: Flow chart of selection of systematic reviews for analysis

3.1.3 Methodological Quality Assessment Tool

The quality of the methodology used in the systematic reviews was assessed using the AMSTAR-2, which is a critical appraisal tool for systematic reviews of randomized control trials (RCT) and/or observational studies (13) The AMSTAR-2 tool contains a set of 16 domains, 7 of which are critical domains and 9 are non-critical (Table 6). A more thorough and specific interpretation of the questions has been published (Supplementary appendix 1: AMSTAR 2 guidance document) (13). A Yes, No, or Partial yes were used to score each of the reviews across all 16 domains. N/A was used when meta-analyses were not conducted. The AMSTAR-2 tool

groups the quality of the systematic reviews into four categories: high, moderate, low, and critically low (Table 7). We scored each entry using the AMSTAR-2 tool and discussed the highest quality results.

Table 6: AMSTAR-2 questionnaire for evaluation of the quality of systematic reviews (13)*. Bolded items represent critical domains. Non-bolded items represent non-critical domains.*

Item 1	Did the research questions and inclusion criteria include components of PICO?
Item 2	Was the protocol registered before the start of the review?
Item 3	Was the selection of the study design for inclusion in the review explained?
Item 4	Is the literature search adequate?
Item 5	Was the study selection performed in duplicate?
Item 6	Was the data extraction performed in duplicate?
Item 7	Is justification provided for excluded individual studies?
Item 8	Were the studies included described in adequate detail?
Item 9	Is the risk of bias from individual studies included in the review?
Item 10	Were the sources of funding reported for the studies included in the review?
Item 11	If applicable, is the meta-analytical method appropriate?
Item 12	If applicable, was the impact of risk of bias in individual studies assessed in meta-analysis or other evidence synthesis?
Item 13	Is the risk of bias considered when interpreting the results of the review?
Item 14	Was a satisfactory explanation and discussion provided for any heterogeneity observed in the results?
Item 15	Is the impact of likely publication bias assessed?
Item 16	Were any potential conflicts of interest reported for conducting the review?

Table 7: Rules for rating the quality of the systematic review based on the AMSTAR-2 tool

Quality of Review	**Basis for assessment**
High	No or one non-critical weakness
Moderate	Two or more non-critical weaknesses
Low	One critical flaw with or without non-critical weaknesses
Critically Low	Two or more critical flaws

3.2 Results of literature search

In order to focus our analysis on the most relevant drugs, we decided to include within our scope only those that have received either full, emergency use authorization, or recommended for use by various regulatory agencies throughout the world (Table 8).

Table 8: List of therapeutics authorized for use by the various regulatory bodies around the world for the treatment of COVID-19

Drug	Category	US	EU	Japan	Rest of World
Remdesivir	Repurposed	✓	✓	✓	✓ *
Baricitinib	Repurposed	✓			
Dexamethasone**	Repurposed	✓	✓	✓	✓ *
Convalescent Plasma	New	✓			
Bamlanivimab or Bamlanivimab & etesevimab	New	✓	Under review		✓ ***
Casirivimab & Imdevimab	New	✓	Under review		✓ ***

*Checkmark on the Rest of World are based on a list of countries for which we found information on drug approvals for COVID-19 use (Australia, Singapore, Canada, India, South Korea, Taiwan, Israel). It is not meant to be comprehensive as information is not available for all the countries of the world.

**Dexamethasone is used to treat symptoms of COVID-19 and does not have special authorization for use against COVID-19 as it is not used to treat the virus itself. Rather it is used to reduce systemic inflammation for which it already has full approval.

***In Canada

The overview of systematic reviews was thus focused on the analysis of the safety and efficacy of the therapeutics noted in the table above.

3.2.1 Remdesivir

As shown in Section 0, remdesivir is expected to work by inhibiting the virus replication. To evaluate whether it has been effective in treating COVID-19 patients, 21 articles were identified to be systematic reviews with or without meta-analysis on the therapeutic effect of remdesivir on COVID-19 patients (86–106). Using the AMSTAR 2 tool, we analyzed the quality of the methodology used to assess these reviews and found that 19% (4/21) were high quality, 10% (2/20) moderate quality, 19% (4/21) low quality and the rest, i.e. 52% (11/21) were critically low quality. Hence, we focused our analysis only on the four high-quality systematic reviews and their associated conclusions (Table 9). Specifically, they agreed on some of remdesivir's clinical effects in treating COVID-19 patients and disagreed on others. There was however no clinical evidence where all four systematic reviews agreed on. The certainty of evidence was also reported based on

the risk of biases such as bias due to randomization, bias due to deviation from intended interventions, bias due to missing data, bias due to outcome measurement, or bias due to selection of reported results.

Table 9: Summary of clinical outcomes of remdesivir based on four high-quality systematic reviews

Remdesivir vs. Placebo	**Misra et al.** (103) **Relative Effect**	**Juul et al.** (104) **Relative Effect**	**Siemieniuk et al.** (88) **Relative Effect**	**Wang et al.** (91) **Relative Effect**
Reduced mortality rate?	No difference	No difference*	No difference*	Yes, in first 14 days of severe cases but not in 28 days
Fewer non-serious adverse effects?	No difference**	No difference*	No difference**	Yes**
Fewer serious adverse effects?		Yes*		
Shortened time to recovery?	No difference	Yes*	No difference*	No difference
Improved chances of recovery?	Yes	N/A	No difference*	No difference

*Low or very low certainty

**Analysis of adverse events was not separated by degree of severity

Summarizing the conclusions from these four systematic reviews, remdesivir does not appear to improve mortality. This is also in agreement with the latest interim data from the SOLIDARITY trial, a WHO-sponsored randomized clinical trial which tested remdesivir on 2750 hospitalized patients in 30 countries (107). Similarly, remdesivir does not seem to increase chances of adverse effects and it may indeed help reduce serious adverse effects. However, it is important to note that some conclusions from the systematic reviews had low to very low certainty. Thus, potential benefits remain to be investigated with further clinical studies. Furthermore, when analyzing result from specific subgroups, such as for example younger patients with no co-morbidities, the data showed a potential benefit to using remdesivir (107). These results are in alignment with the

National Institutes of Health (NIH) guidelines which recommend prescribing remdesivir to hospitalized patients requiring supplemental oxygen but not those on a mechanical ventilator (108). In line with the rationale above, the NIH guideline has a "moderate" rating on the remdesivir recommendation.

3.2.2 Baricitinib

As discussed in Section 0, Baricitinib is a JAK inhibitor. JAKs are transmembrane proteins that relay extracellular signals from growth factors and cytokines. Inhibitors of JAKs have been effective in the treatment of inflammatory diseases (109) and may be useful against high levels of cytokines and inflammation seen in patients with severe COVID-19 disease (110). Only 3 systematic reviews were found that evaluate whether it has been effective in treating COVID-19 patients (101,111,112). One of the articles was of moderate quality and the other two were of critically low quality. No articles were of a high quality. Therefore, we evaluated the results of the moderate quality study (Table 10) and compared its conclusions to recommendations by regulatory agencies.

Table 10: Summary of clinical outcomes of baricitinib based on one moderate systematic review

Baricitinib vs. Placebo	**Walz et al.** (111) **Relative Effect**
Reduced mortality rate?	Yes
Fewer non-serious adverse effects?	N/A
Fewer serious adverse effects?	
Shortened time to recovery?	Yes
Improved chances of recovery?	Yes

The conclusions by Walz et al. suggest that baricitinib is effective at treating COVID-19 patients in terms of reducing the risk of death as well as improving their clinical outcomes and the time to reach beneficial clinical outcomes. It should be noted that the number of patients used in

the corresponding meta-analysis is very low and patient heterogeneity was limited. According to the NIH there are insufficient data to clarify the role of baricitinib in the management of COVID-19 (113). However, based on the adaptive ACTT-2 trial where baricitinib was prescribed in combination with remdesivir on patients who had developed pneumonia, NIH recommends against the use of baricitinib in the absence of remdesivir. But, due to insufficient data, it does not make a recommendation for or against the use of baricitinib in combination with remdesivir. Similarly, when prescribed in combination with dexamethasone or other corticosteroids, a recommendation for or against the use of baricitinib could not be made due to insufficient data.

3.2.3 Dexamethasone

Dexamethasone is a generic prescription corticosteroid that is administered to reduce systemic inflammation. As COVID-19 is associated with an inflammatory response by the body that can potentially lead to organ damage (e.g., lung injury, multisystem organ dysfunction), there is a rationale to using dexamethasone in such patients. Dexamethasone is the preferred corticosteroid due to its longer half-life relative to other corticosteroids (e.g., hydrocortisone, prednisone, methylprednisolone) and thus its ease of administration once daily as opposed to several times a day. However, in its absence, other corticosteroids can be used as a replacement (114). 21 systematic reviews were retrieved from our search that discuss the effect of dexamethasone in treating COVID-19 patients (70,88,92,96,101,102,104,115–128). 6/21 (29%) were high quality, 10/21 (47%) were low quality and 5/21 (24%) were critically low-quality reviews. A select few studies do not specify which corticosteroids were used, in which case we included them as well, under the assumption that the effect of all corticosteroids is expected to be similar.

A total of 6 systematic reviews were considered of high quality. Two of the high-quality systematic reviews did not conduct a meta-analysis of all the clinical data reported and results were thus discussed as a narrative review summarizing the conclusions from each study rather than a comprehensive summary of all the clinical evidence (70)(118). Consequently, these reviews were not included in our analysis. Similar to the overview of remdesivir, the four high quality systematic reviews on dexamethasone in the context of COVID-19 were not consistent on clinical benefits of dexamethasone (Table 11).

Table 11: Summary of clinical outcomes of dexamethasone based on four high systematic reviews

Dexamethasone vs. Placebo	**Sterne et al.** (126) **Relative Effect**	**Juul et al.** (78) **Relative Effect**	**Siemieniuk et al.** (88) **Relative Effect**	**Cheng et al.** (117) **Relative Effect****
Reduced mortality rate?	Yes, in critically ill patients	Yes, in critically ill patients*	Yes	No difference*
Fewer non-serious adverse effects?	N/A	N/A	N/A	No, worse effects*
Fewer serious adverse effects?	Yes, in critically ill patients	Yes, in critically ill patients*	N/A	N/A
Shortened time to recovery?	N/A	N/A	No difference*	Yes*
Improved chances of recovery?	N/A	N/A	N/A	Yes*

*Low certainty

**No randomized controlled trials were included in this article.

The biggest contrast in results stemmed from the study by Cheng et al. Specifically, this report did not contain randomized controlled trials but only included cohort studies with and without controls. This factor is a likely reason for the discrepancy in conclusions between this review and the other three. Additionally, majority of the data used in the analysis of the three other reviews was from the WHO-sponsored RECOVERY trial with a total of 2104 patients randomized

for the dexamethasone arm. The most beneficial result agreed upon by all three reviews was on the effect of dexamethasone in improving clinical symptoms of critically ill patients and consequently reducing the mortality rate. It is important to note that the risk of serious adverse effects is considered smaller in the dexamethasone treated patients in the studies by Sterne et al. and Juul et al. because of the reduced deaths. While it was not explicitly stated in the report, this is a likely conclusion for the Siemieniuk et al. study as well. In line with these results, the guidance by regulatory agencies, is to administer dexamethasone to hospitalized COVID-19 patients receiving supplemental oxygenation or who are on mechanical ventilation or Extracorporeal Membrane Oxygenation (ECMO) (114). The effect on mild cases of COVID-19 is not beneficial in reducing deaths and could be associated with more adverse effects than the standard of care such as hypertension, weight gain, diabetes, psychiatric and psychological effects, osteoporosis etc. (129).

3.2.4 Convalescent plasma

After infection and recovery from COVID-19, many people develop immunity to the disease as antibodies found in their blood plasma. COVID-19 antibody containing plasma from these patients, can be donated to produce a) convalescent plasma or b) hyper immunoglobulin (a more concentrated preparation that contains more antibodies). Based on the search of systematic reviews outlined in section 3.1, we identified 13 articles, 3 of which were high quality (23%), 6 were low quality (46%), and 4 were critically low quality (31%) (91,92,94,96,102,104,130–136). The three high quality systematic reviews on convalescent plasma were in agreement that the data were insufficient to provide definite conclusions on the clinical benefits of convalescent plasma in treating COVID-19 patients. The results from their analyses are summarized in (Table 12).

Table 12: Summary of clinical outcomes of convalescent plasma based on three high quality systematic reviews.

Convalescent Plasma vs. Placebo	**Piechotta et al.** (135) **Relative Effect***	**Juul et al.** (78) **Relative Effect**	**Wang et al.** (91) **Relative Effect**
Reduced mortality rate?	Inconclusive	No difference*	Yes, in severe cases*
Fewer non-serious adverse effects?	Inconclusive	N/A	N/A
Fewer serious adverse effects?	Inconclusive	N/A	N/A
Shortened time to recovery?	Inconclusive	N/A	N/A
Improved chances of recovery?	Inconclusive	N/A	N/A

*Very low certainty

All three systematic reviews were published on or prior to July 2020 and analyses were conducted based on data available at the time, specifically from one randomized clinical trial, several non-randomized clinical trials, and/or case studies. At the time of this writing (January 2021), seven additional RCTs have been completed and corresponding data published (reference them all). In the absence of a systematic review and meta-analysis of all RCTs, we report conclusions (Table 13) from a living database, covid-nma.com, which is an international initiative associated with the WHO lead by a team of researchers from Cochrane and a broad multidisciplinary consortium of universities, hospitals, and foundations.

Table 13: Summary of conclusions on convalescent plasma from the covid-nma living database

Convalescent Plasma vs. Placebo	**Relative effect**	**Certainty of evidence**
Reduced mortality rate?	Yes, by day 7; No difference by day 14-28	Moderate
Fewer non-serious adverse effects?	No difference	Moderate
Fewer serious adverse effects?	No difference	Low
Shortened time to recovery?	No difference	Low
Improved chances of recovery?	N/A	N/A

In summary, with no worsening adverse effects, convalescent plasma may be beneficial in reducing the mortality rate in COVID-19 patients as long as it is administered early on. As the number of patients in these clinical trials is not large enough, such as for example in the case of

the WHO-funded SOLIDARITY trial, the certainty of conclusions on the utility of convalescent plasma in a therapeutic effect is limited.

3.2.5 Neutralizing antibodies therapy

3.2.5.1 Bamlanivimab

Bamlanivimab, also known as LY-CoV555 or LY3819253, was approved by the US FDA under emergency use in November 2020 for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients and who are at high risk for progressing to severe COVID-19 (137). No systematic reviews were found on the safety and efficacy of bamlanivimab. However, results from two randomized controlled clinical trials, specifically BLAZE-1 and BLAZE-2 trials, have recently been published.

Results from the BLAZE-1 interim analysis from 452 patients in September 2020 showed that bamlanivimab reduced the viral load more significantly than placebo for one of the doses tested (138). Similarly, patients who were treated with the antibody showed slightly decreased severity of symptoms than those who received placebo. Final analysis of the BLAZE-1 trial, which randomized 577 patients concluded that bamlavinimab alone did not significantly reduce viral load, unlike what had been reported in the interim results. However, the BLAZE-1 trial also included a combination therapy of bamlavinimab and etesvimab, another neutralizing antibody that binds to the SARS-CoV-2 surface spike protein receptor binding domain. Results from this combination therapy showed that the cocktail of bamlavinimab and etesvimab did significantly reduce SARS-CoV-2 viral load at day 11 when compared to placebo (139). Furthermore, data from the Phase 3 BLAZE-1 trial showed that bamlanivimab and etesevimab together reduced the risk of COVID-19 hospitalizations and death. As a result, in February 2021, the FDA granted

Emergency Use Authorization (EUA) for bamlanivimab and etesevimab administered together to treat mild to moderate COVID-19 in patients 12 years and older who are at high risk for progressing to severe COVID-19 and/or hospitalization. (140). The BLAZE-2 trial is a Phase 3 prevention clinical trials which is ongoing and aims to evaluate whether otherwise healthy residents and staff at long-term care facilities have a reduced risk of contracting COVID-19. Results from this study are not yet published in peer reviewed journals but are suggestive of positive effects in reducing the risk of contracting symptomatic COVID-19 as announced by Eli Lilly, the manufacturer of bamlanivimab (141).

3.2.5.2 Casirivimab & Imdevimab antibody cocktail

Similar to bamlanivimab and etesevimab, casirivimab and imdevimab, also known as REGN-COV2, is a cocktail of two antibodies, that was approved by the US FDA under emergency use in November 2020 for the treatment of mild to moderate COVID-19 in adults and pediatric patients who are at high risk for progressing to severe COVID-19 (142). As of the date of our database search (November 21, 2020) no systematic reviews had been published on the safety and efficacy of REGN-COV2. However, interim results from an ongoing RCT were published in January 2021 and showed that for 275 symptomatic non-hospitalized patients the REGN-COV2 antibody cocktail reduced viral load on those patients who did not have an immune response yet (as measured by an antibody test) or those who had a high viral load at baseline. Additionally, the safety profile of the antibody cocktail was similar to placebo (143).

3.3 Discussion of Findings

Using highly rated systematic reviews is a good way to funnel the myriad reviews and articles about COVID-19 and minimize bias in order to potentially extract the most appropriate evidence

generated so far with regards to COVID-19 treatments. In general, only ~20% of systematic reviews were of high quality. Nonetheless, this number is higher than what was previously reported in early 2020 for systematic reviews on COVID-19 (144), and could be explained by the fact that there may be an improvement in data quality over time.

Due to the rapidly evolving scientific evidence for treatments, systematic reviews can be limiting because they take time to prepare and become available in peer reviewed journals. That is why living systematic reviews and databases can be complimentary tools in order to elucidate the most accurate picture of the current landscape. Indeed, as noted in the sections above, we utilized these resources, supplemented with guidance from government agencies (e.g., NIH) and non-governmental agencies (e.g., WHO). Due to the recurrent nature of this process, data assessment and reassessment is inherent in formulating and updating the treatment guidance.

As was noted on the discussions on baricitinib and convalescent plasma, there is no consensus for or against use of these therapeutics at this point in time. Differently designed RCTs and longer data maturity may help clarify the benefits in the future. Also, real world data, wherein scientist can evaluate the effects of these treatments, may help further evaluate their benefits or lack thereof. Last but not least, it is critical that regulatory bodies such as the FDA, WHO, NIH and other ones around the world frequently update their guidelines as more evidence emerges.

4 Emerging challenges from new COVID-19 variants

"Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world." – Louis Pasteur

As noted previously, while repurposed drugs do not appear to show significant effect in ameliorating clinical symptoms of COVID-19 with the exception of dexamethasone which reduces the risk of death in severe cases, monoclonal antibodies appear to be showing some promise. Nonetheless, there are several significant challenges as of the time of this writing that will become more prevalent in the near future that may reduce the efficacy of these antibodies. Specifically, there are rightful concerns about emerging SARS-CoV-2 mutations which can render these antibodies ineffective (145). For example, one study in Cell concluded that up to 10 mutations such as N234Q, L452R, A475V and V483A were resistant to some neutralizing monoclonal antibodies in development (146). Furthermore, recently more virulent COVID-19 strains have been detected and proliferating around the world (147). For example, lineage N501Y.V1 (also called B.1.1.7) is a cluster of infections that rapidly spread in southeastern England and had amassed 17 mutations before detection. Eight of these mutations are in the spike glycoprotein, including N501Y in the RBD, and they could potentially influence the ACE2 binding and viral replication. Similarly, a different variant also with an N501Y mutation, is rapidly spreading in South Africa (148). This new variant from South Africa is known as the N501Y.V2 variant (or B.1.351) and seems to be a close relative of a lesser-known variant found in Brazil (P.1).

The N501Y.V2 strain has caused more concerns since it has significantly more mutations than previous strains which are close to the RBD and may also affect the binding site of the neutralizing monoclonal antibodies (149). One recent study (not peer reviewed) showed that the SARS-CoV-2 501Y.V2 variant, completely evades three different classes of relevant antibodies

as well as antibodies found in COVID-19 convalescent plasma (150). In response to the new ability of new strains to overcome the neutralizing effect of antibodies, bamlanivimab is now being tested in combination with another antibody VIR-7831 (also known as GSK4182136) in its BLAZE-4 clinical trial in low-risk patients with mild to moderate COVID-19. This combination therapy is expected to be more effective as the two neutralizing antibodies bind to different epitopes of the SARS-CoV-2 spike protein (151).

As of the time of this writing, the US FDA has approved two vaccines shown to be effective against the wild type SARS-CoV-2. It was an amazing scientific feat that a transatlantic collaboration between Pfizer (U.S.) and BioNTech (Germany) followed by Moderna (U.S.), in close collaboration with the wider medical and scientific community announced in late 2020 that they had succeeded in producing a safe and >90% effective vaccine against the original COVID-19 strain in record time (152)(153). It is important to note that the Pfizer-BioNTech and Moderna vaccines are both based on novel mRNA technology which makes them the first therapeutic products of this type in the market (154). Vaccination programs have started around the world and in Israel, the country leading the world in vaccination efforts, positive trends in the decrease of new cases have been observed, particularly in 60+ age patients (155). While these preliminary results suggest that vaccines can be effective tools in the battle against COVID-19, they are designed against the spike protein, and as a result can have reduced efficacy against the new COVID-19 variants. Indeed, one study has shown that mutations in the RBD of the N501Y.V2 variant reduces the neutralizing efficiency of antibodies induced by mRNA vaccines in the laboratory, whereas another study has shown that the Moderna mRNA vaccine is about 6-fold less effective against the N501Y.V2 variant in human sera (149).

In summary, there remains a high unmet medical need to continue discovering and developing new therapeutics as well as new or modified versions of vaccines. Furthermore, there still remains an unmet medical need for what are known as long coviders, who have contracted COVID-19 in the past and have recovered, but with many ongoing health symptoms remaining and recuring long after the original infection and recovery.

5 Conclusions

"Discipline is the bridge between goals and accomplishment." – Mother Teresa

A variety of repurposed and novel drugs have been developed and investigated in clinical trials for treatment of COVID-19 patients. The clinical outcomes from such trials that are reported in peer reviewed scientific journals are often inconsistent. Just to name a few examples, tocilizumab was shown to improve survival in some publications (156–158) and was shown to have no effect on survival in some others (159–161). Similarly, remdesivir was shown to have a mortality benefit in one publication (162) and no benefit in another (107). These inconsistencies have stemmed in part from the enormous amount of literature published during this time and partly from the limited amount of clinical data available at the time of publication. Thus, it was not trivial to properly assess the clinical benefits of a particular therapeutic without a thorough evaluation of the statistics and risk of bias of the data that informed the authors' conclusions. Systematic reviews offered a mechanism by which this data was carefully evaluated. Most systematic reviews follow certain guidelines in order to report the information necessary for the reader to assess strengths and weaknesses of the investigation (163) and consequently of its conclusions. We used AMSTAR-2, a methodological protocol to determine the quality of systematic reviews (13). It was notable that SARS-CoV-2 related systematic reviews had particularly poor compliance with the guidelines (only ~20% were high quality). While one might rationalize the poor compliance of systematic reviews by the urgency and necessity to make the information available as quickly as possible, the need for speed must not come at the expense of accuracy and a high standard in order to provide the most reliable information and insights to the scientific and clinical community.

After selecting and analyzing the highest quality articles based on the AMSTAR-2 methodology, one of our main conclusions was that out of the drugs we evaluated, only dexamethasone was proven effective at reducing the mortality rate in severe cases. All other drugs have had inconclusive outcomes. For novel drugs (e.g., neutralizing monoclonal antibodies) systematic reviews were not available. Thus, we only analyzed the latest available published data/reports/news. Our second main conclusion was that neutralizing monoclonal antibodies are showing promise in treating patients early in the disease stage. However, clinical trials are still ongoing and the final data for some of them are not available yet.

While the AMSTAR-2 tool is helpful in filtering the highest quality systematic reviews and thus providing conclusions that are based on a thorough evaluation of the evidence, findings from its usage cannot be formulated in vacuum and need to be triangulated with those from serious scientific organizations like NIH in order to be validated. In addition to the main conclusions some other takeaways and recommendations from our thesis work include:

1) Despite the negative preclinical evidence or lack of it for some antiviral repurposed drugs, clinical trials nonetheless were still pursued. Perhaps a better approach for the future would be that such drugs do not get pursued further and limited resources get diverted to more promising candidates. Since, preclinical evidence generation is fast relative to clinical, it should be pursued first.
2) Although it is early to have a final call, novel drugs appear to be effective and they should be pursued in parallel even though they take longer to be approved compared to repurposed drugs. Additionally, while beyond the scope of this thesis, administration and global access of such novel drugs will be a challenge.

3) An effective framework has been developed by regulatory agencies to help speed the development of therapeutics (e.g., the ACTIV program) and can serve as a blueprint for future epidemics/pandemics.

As clinical trials continue and more mature data is reported, conclusive results on the clinical benefits of the drugs discussed in this thesis are expected to become available. Similarly, new therapeutics that are currently in early development and consequently not discussed here may prove beneficial in treating SARS-CoV-2 and it's emerging more transmissible and resistant new variants. Thus, as a continuation of our work, keeping up with the latest clinical evidence and corresponding meta-analyses and data interpretation is critical in order to update the COVID-19 therapeutic landscape. Various databases have been recently developed that can help in this endeavor (e.g., the WHO associated www.covid-nma.com).

Lastly, when the worst of this pandemic is over, it will be important to assess from a systems-based viewpoint all the interactions between the different healthcare system components to understand what worked and what didn't work in the fight against COVID-19. Specifically, building a stakeholder map with the appropriate value flows (e.g., regulatory, monetary, technology) would help visualize the relationships between stakeholders and their interactions. After building this static view, a system dynamic model can be developed to elucidate the best strategies, tools and mechanisms that helped speed up therapeutic/vaccine development in the current pandemic and inform potential best practices for the future.

"One day, we will be able to gather again together without thinking twice. But to get there, we must continue to pull together – keeping our distance, keeping our masks on and keeping each other safe – until every member of our community is protected from Covid-19."

L. Rafael Reif - President of the Massachusetts Institute of Technology

6 Appendix - Database Search Queries

Embase database search:
('covid 19':ab,ti OR 'sars cov 2':ab,ti OR '2019 ncov':ab,ti) AND (treatment:ab,ti OR therapeutics:ab,ti) AND ('systematic review':ab,ti OR 'meta analysis':ab,ti)

PubMed database search:

((covid 19[Title/Abstract]) OR (sars cov 2[Title/Abstract]) OR (2019 ncov[Title/Abstract])) AND ((treatment[Title/Abstract]) OR (therapeutics[Title/Abstract])) AND ((systematic review[Title/Abstract]) OR (meta analysis[Title/Abstract]))

Cochrane Library Database search:

Covid 19 title, abstract, keywords limited to Cochrane Reviews

Medline: (TS=(covid 19) OR TS=(sars cov 2) OR TS=(2019 ncov)) AND (TS=(treatment) OR TS=(therapeutic)) AND (TS=(systematic review) OR TS=(meta analysis))
Refined by: LANGUAGES: (ENGLISH) AND PUBLICATION TYPES: (JOURNAL ARTICLE OR SYSTEMATIC REVIEW OR REVIEW OR META ANALYSIS)
Timespan: Last 5 years.

7 References

1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med [Internet]. 2020/01/29. 2020 Mar 26;382(13):1199–207. Available from: https://pubmed.ncbi.nlm.nih.gov/31995857
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med [Internet]. 2020 Jan 24;382(8):727–33. Available from: https://doi.org/10.1056/NEJMoa2001017
3. Fauci AS, Lane HC, Redfield RR. Covid-19 — Navigating the Uncharted. N Engl J Med [Internet]. 2020 Feb 28;382(13):1268–9. Available from: https://doi.org/10.1056/NEJMe2002387
4. Mohapatra RK, Pintilie L, Kandi V, Sarangi AK, Das D, Sahu R, et al. The recent challenges of highly contagious COVID-19, causing respiratory infections: Symptoms, diagnosis, transmission, possible vaccines, animal models, and immunotherapy. Chem Biol Drug Des [Internet]. 2020/07/26. 2020 Nov;96(5):1187–208. Available from: https://pubmed.ncbi.nlm.nih.gov/32654267
5. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed. 2020 Mar;91(1):157–60.
6. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis [Internet]. 2020 May 1 [cited 2021 Jan 5];20(5):533–4. Available from: https://www.who.int/china/news/
7. Max Roser, Hannah Ritchie EO-O and JH. Coronavirus Pandemic (COVID-19). Our

World Data [Internet]. 2020; Available from: https://ourworldindata.org/coronavirus

8. Centers for Disease Control and Prevention. Flu Burden and Flu Burden Averted by Vaccination Infographic [Internet]. 2019 [cited 2021 Feb 9]. Available from: https://www.cdc.gov/flu/resource-center/freeresources/graphics/infographic-averted-17-18.htm

9. He J, Guo Y, Mao R, Zhang J. Proportion of asymptomatic coronavirus disease 2019: A systematic review and meta-analysis. J Med Virol [Internet]. 2021 Feb 1;93(2):820–30. Available from: https://doi.org/10.1002/jmv.26326

10. Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries. PLoS One [Internet]. 2020 Jun 23;15(6):e0234765–e0234765. Available from: https://pubmed.ncbi.nlm.nih.gov/32574165

11. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA [Internet]. 2020 Aug 25;324(8):782–93. Available from: https://doi.org/10.1001/jama.2020.12839

12. Petersen E, Koopmans M, Go U, Hamer DH, Petrosillo N, Castelli F, et al. Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. Lancet Infect Dis [Internet]. 2020 Sep 1;20(9):e238–44. Available from: https://doi.org/10.1016/S1473-3099(20)30484-9

13. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical

appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ [Internet]. 2017;358. Available from: https://www.bmj.com/content/358/bmj.j4008

14. Biorender. COVID-19 Vaccine & Therapeutics Tracker [Internet]. 2021 [cited 2021 Feb 8]. Available from: https://biorender.com/covid-vaccine-tracker

15. Thu Van Nguyen, Gabriel Ferrand, Sarah Cohen-Boulakia, Ruben Martinez, Philipp Kapp, Emmanuel Coquery … for the COVID-NMA consortium. (2020). RCT studies on preventive measures and treatments for COVID-19 [Data set]. Zenodo. [Internet]. 2020. Available from: http://doi.org/10.5281/zenodo.4266529

16. Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, et al. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov [Internet]. 2019;18(1):41–58. Available from: https://doi.org/10.1038/nrd.2018.168

17. Boran ADW, Iyengar R. Systems approaches to polypharmacology and drug discovery. Curr Opin Drug Discov Devel [Internet]. 2010 May;13(3):297–309. Available from: https://pubmed.ncbi.nlm.nih.gov/20443163

18. Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, et al. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol [Internet]. 2020;5(4):536–44. Available from: https://doi.org/10.1038/s41564-020-0695-z

19. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet [Internet]. 2020 Feb 22;395(10224):565–74. Available from:

https://doi.org/10.1016/S0140-6736(20)30251-8

20. Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, et al. A new coronavirus associated with human respiratory disease in China. Nature [Internet]. 2020;579(7798):265–9. Available from: https://doi.org/10.1038/s41586-020-2008-3

21. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature [Internet]. 2020;579(7798):270–3. Available from: https://doi.org/10.1038/s41586-020-2012-7

22. Yoshimoto FK. The Proteins of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2 or n-COV19), the Cause of COVID-19. Protein J [Internet]. 2020;39(3):198–216. Available from: https://doi.org/10.1007/s10930-020-09901-4

23. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020 Mar;14(1):72–3.

24. Xiu S, Dick A, Ju H, Mirzaie S, Abdi F, Cocklin S, et al. Inhibitors of SARS-CoV-2 Entry: Current and Future Opportunities. J Med Chem [Internet]. 2020 Nov 12;63(21):12256–74. Available from: https://doi.org/10.1021/acs.jmedchem.0c00502

25. Ojha PK, Kar S, Krishna JG, Roy K, Leszczynski J. Therapeutics for COVID-19: from computation to practices—where we are, where we are heading to. Mol Divers [Internet]. 2021;25(1):625–59. Available from: https://doi.org/10.1007/s11030-020-10134-x

26. Kramer VG, Schader SM, Oliveira M, Colby-Germinario SP, Donahue DA, Singhroy DN, et al. Maraviroc and Other HIV-1 Entry Inhibitors Exhibit a Class-Specific Redistribution Effect That Results in Increased Extracellular Viral Load. Antimicrob Agents Chemother

[Internet]. 2012 Aug 1;56(8):4154 LP – 4160. Available from: http://aac.asm.org/content/56/8/4154.abstract

27. Sweiti H, Ekwunife O, Jaschinski T, Lhachimi SK. Repurposed Therapeutic Agents Targeting the Ebola Virus: A Systematic Review. Curr Ther Res [Internet]. 2017;84:10–21. Available from: http://www.sciencedirect.com/science/article/pii/S0011393X16301229

28. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res [Internet]. 2020/02/04. 2020 Mar;30(3):269–71. Available from: https://pubmed.ncbi.nlm.nih.gov/32020029

29. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov [Internet]. 2020;6(1):16. Available from: https://doi.org/10.1038/s41421-020-0156-0

30. Bestle D, Heindl MR, Limburg H, Van Lam van T, Pilgram O, Moulton H, et al. TMPRSS2 and furin are both essential for proteolytic activation of SARS-CoV-2 in human airway cells. Life Sci alliance [Internet]. 2020 Jul 23;3(9):e202000786. Available from: https://pubmed.ncbi.nlm.nih.gov/32703818

31. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell [Internet]. 2020;181(2):271-280.e8. Available from: http://www.sciencedirect.com/science/article/pii/S0092867420302294

32. Hoffmann M, Schroeder S, Kleine-Weber H, Müller MA, Drosten C, Pöhlmann S. Nafamostat Mesylate Blocks Activation of SARS-CoV-2: New Treatment Option for COVID-19. Antimicrob Agents Chemother [Internet]. 2020 May 21;64(6):e00754-20. Available from: http://aac.asm.org/content/64/6/e00754-20.abstract

33. Funnell SGP, Dowling WE, Muñoz-Fontela C, Gsell P-S, Ingber DE, Hamilton GA, et al. Emerging preclinical evidence does not support broad use of hydroxychloroquine in COVID-19 patients. Nat Commun [Internet]. 2020;11(1):4253. Available from: https://doi.org/10.1038/s41467-020-17907-w

34. Gilmore K, Zhou Y, Ramirez S, Pham L V, Fahnøe U, Feng S, et al. In vitro efficacy of Artemisinin-based treatments against SARS-CoV-2. bioRxiv [Internet]. 2020 Jan 1;2020.10.05.326637. Available from: http://biorxiv.org/content/early/2020/10/05/2020.10.05.326637.abstract

35. Shrimp JH, Kales SC, Sanderson PE, Simeonov A, Shen M, Hall MD. An Enzymatic TMPRSS2 Assay for Assessment of Clinical Candidates and Discovery of Inhibitors as Potential Treatment of COVID-19. ACS Pharmacol Transl Sci [Internet]. 2020 Oct 9;3(5):997–1007. Available from: https://doi.org/10.1021/acsptsci.0c00106

36. Okamoto M, Toyama M, Baba M. The chemokine receptor antagonist cenicriviroc inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020 Oct;182:104902.

37. Wang X, Cao R, Zhang H, Liu J, Xu M, Hu H, et al. The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 in vitro. Cell Discov [Internet]. 2020;6(1):28. Available from: https://doi.org/10.1038/s41421-020-0169-8

38. Saheb Sharif-Askari N, Saheb Sharif-Askari F, Al Heialy S, Hamoudi R, Kashour T,

Hamid Q, et al. Cardiovascular medications and regulation of COVID-19 receptors expression. Int J Cardiol Hypertens [Internet]. 2020 Jun 6;6:100034. Available from: https://pubmed.ncbi.nlm.nih.gov/33447763

39. Alnajjar R, Mostafa A, Kandeil A, Al-Karmalawy AA. Molecular docking, molecular dynamics, and in vitro studies reveal the potential of angiotensin II receptor blockers to inhibit the COVID-19 main protease. Heliyon. 2020 Dec;6(12):e05641.

40. Nejat R, Sadr AS, Freitas B, Crabtree J, Pegan S, Tripp R, et al. Losartan promotes cell survival following SARS-CoV-2 infection in vitro [Internet]. bioRxiv; 2020. Available from: http://europepmc.org/abstract/PPR/PPR258698

41. Shamsi A, Mohammad T, Anwar S, AlAjmi MF, Hussain A, Rehman MT, et al. Glecaprevir and Maraviroc are high-affinity inhibitors of SARS-CoV-2 main protease: possible implication in COVID-19 therapy. Biosci Rep [Internet]. 2020 Jun 2;40(6). Available from: https://doi.org/10.1042/BSR20201256

42. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA [Internet]. 2020 May 12;323(18):1824–36. Available from: https://doi.org/10.1001/jama.2020.6019

43. Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, et al. Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. ACS Cent Sci [Internet]. 2020 May 27;6(5):672–83. Available from: https://doi.org/10.1021/acscentsci.0c00489

44. Mulangu S, Dodd LE, Davey RTJ, Tshiani Mbaya O, Proschan M, Mukadi D, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med. 2019

Dec;381(24):2293–303.

45. Pruijssers AJ, George AS, Schäfer A, Leist SR, Gralinksi LE, Dinnon KH 3rd, et al. Remdesivir Inhibits SARS-CoV-2 in Human Lung Cells and Chimeric SARS-CoV Expressing the SARS-CoV-2 RNA Polymerase in Mice. Cell Rep. 2020 Jul;32(3):107940.

46. Choy K-T, Wong AY-L, Kaewpreedee P, Sia SF, Chen D, Hui KPY, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral Res [Internet]. 2020;178:104786. Available from: http://www.sciencedirect.com/science/article/pii/S016635422030200X

47. Ma C, Sacco MD, Hurst B, Townsend JA, Hu Y, Szeto T, et al. Boceprevir, GC-376, and calpain inhibitors II, XII inhibit SARS-CoV-2 viral replication by targeting the viral main protease. Cell Res [Internet]. 2020;30(8):678–92. Available from: https://doi.org/10.1038/s41422-020-0356-z

48. De Meyer S, Bojkova D, Cinatl J, Van Damme E, Buyck C, Van Loock M, et al. Lack of antiviral activity of darunavir against SARS-CoV-2. Int J Infect Dis [Internet]. 2020 Aug 1;97:7–10. Available from: https://doi.org/10.1016/j.ijid.2020.05.085

49. BioSpace. J&J Says HIV Drug Darunavir Hasn't Been Proven to be Effective for COVID-19 Treatment [Internet]. 2020 [cited 2021 Feb 11]. Available from: https://www.biospace.com/article/j-and-j-says-hiv-drug-darunavir-hasn-t-been-proven-to-be-effective-for-covid-19-treatment

50. Tan Q, Duan L, Ma Y, Wu F, Huang Q, Mao K, et al. Is oseltamivir suitable for fighting against COVID-19: In silico assessment, in vitro and retrospective study. Bioorg Chem

[Internet]. 2020/09/02. 2020 Nov;104:104257. Available from: https://pubmed.ncbi.nlm.nih.gov/32927129

51. Kaptein SJF, Jacobs S, Langendries L, Seldeslachts L, ter Horst S, Liesenborghs L, et al. Favipiravir at high doses has potent antiviral activity in SARS-CoV-2−infected hamsters, whereas hydroxychloroquine lacks activity. Proc Natl Acad Sci [Internet]. 2020 Oct 27;117(43):26955 LP – 26965. Available from: http://www.pnas.org/content/117/43/26955.abstract

52. Park S-J, Yu K-M, Kim Y-I, Kim S-M, Kim E-H, Kim S-G, et al. Antiviral Efficacies of FDA-Approved Drugs against SARS-CoV-2 Infection in Ferrets. Palese P, editor. MBio [Internet]. 2020 Jun 30;11(3):e01114-20. Available from: http://mbio.asm.org/content/11/3/e01114-20.abstract

53. Raimondi MT, Donnaloja F, Barzaghini B, Bocconi A, Conci C, Parodi V, et al. Bioengineering tools to speed up the discovery and preclinical testing of vaccines for SARS-CoV-2 and therapeutic agents for COVID-19. Theranostics [Internet]. 2020 May 27;10(16):7034–52. Available from: https://pubmed.ncbi.nlm.nih.gov/32641977

54. Fintelman-Rodrigues N, Sacramento CQ, Ribeiro Lima C, Souza da Silva F, Ferreira AC, Mattos M, et al. Atazanavir, Alone or in Combination with Ritonavir, Inhibits SARS-CoV-2 Replication and Proinflammatory Cytokine Production. Antimicrob Agents Chemother [Internet]. 2020 Sep 21;64(10):e00825-20. Available from: https://pubmed.ncbi.nlm.nih.gov/32759267

55. Sacramento CQ, Fintelman-Rodrigues N, Temerozo JR, da Silva Gomes Dias S, Ferreira AC, Mattos M, et al. The in vitro antiviral activity of the anti-

hepatitis C virus (HCV) drugs daclatasvir and sofosbuvir against SARS-CoV-2. bioRxiv [Internet]. 2020 Jan 1;2020.06.15.153411. Available from: http://biorxiv.org/content/early/2020/06/16/2020.06.15.153411.abstract

56. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res [Internet]. 2020;178:104787. Available from: https://www.sciencedirect.com/science/article/pii/S0166354220302011

57. White MA, Lin W, Cheng X. Discovery of COVID-19 Inhibitors Targeting the SARS-CoV-2 Nsp13 Helicase. J Phys Chem Lett [Internet]. 2020 Nov 5;11(21):9144–51. Available from: https://doi.org/10.1021/acs.jpclett.0c02421

58. Liu X, Wang X-J. Potential inhibitors against 2019-nCoV coronavirus M protease from clinically approved medicines. J Genet Genomics [Internet]. 2020/02/13. 2020 Feb 20;47(2):119–21. Available from: https://pubmed.ncbi.nlm.nih.gov/32173287

59. Mostafa A, Kandeil A, A M M Elshaier Y, Kutkat O, Moatasim Y, Rashad AA, et al. FDA-Approved Drugs with Potent In Vitro Antiviral Activity against Severe Acute Respiratory Syndrome Coronavirus 2. Pharmaceuticals (Basel) [Internet]. 2020 Dec 4;13(12):443. Available from: https://pubmed.ncbi.nlm.nih.gov/33291642

60. Wahl A, Gralinski LE, Johnson CE, Yao W, Kovarova M, Dinnon KH, et al. SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801. Nature [Internet]. 2021; Available from: https://doi.org/10.1038/s41586-021-03312-w

61. Tong S, Su Y, Yu Y, Wu C, Chen J, Wang S, et al. Ribavirin therapy for severe COVID-19: a retrospective cohort study. Int J Antimicrob Agents [Internet]. 2020;56(3):106114.

Available from: https://www.sciencedirect.com/science/article/pii/S0924857920302971

62. Li H, Xiong N, Li C, Gong Y, Liu L, Yang H, et al. Efficacy of ribavirin and interferon-α therapy for hospitalized patients with COVID-19: A multicenter, retrospective cohort study. Int J Infect Dis [Internet]. 2021;104:641–8. Available from: https://www.sciencedirect.com/science/article/pii/S1201971221000667

63. Grobler JA, Anderson AS, Fernandes P, Diamond MS, Colvis CM, Menetski JP, et al. Accelerated Preclinical Paths to Support Rapid Development of COVID-19 Therapeutics. Cell Host Microbe. 2020 Nov;28(5):638–45.

64. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Clin Immunol [Internet]. 2020/03/25. 2020 May;214:108393. Available from: https://pubmed.ncbi.nlm.nih.gov/32222466

65. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020 May;130(5):2620–9.

66. Feuillet V, Canard B, Trautmann A. Combining Antivirals and Immunomodulators to Fight COVID-19. Trends Immunol [Internet]. 2021;42(1):31–44. Available from: https://www.sciencedirect.com/science/article/pii/S1471490620302611

67. Hoang TN, Pino M, Boddapati AK, Viox EG, Starke CE, Upadhyay AA, et al. Baricitinib treatment resolves lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques. Cell [Internet]. 2021 Jan 21;184(2):460-475.e21. Available from: https://doi.org/10.1016/j.cell.2020.11.007

68. Hahn F, Wangen C, Häge S, Peter AS, Dobler G, Hurst B, et al. IMU-838, a Developmental DHODH Inhibitor in Phase II for Autoimmune Disease, Shows Anti-SARS-CoV-2 and Broad-Spectrum Antiviral Efficacy In Vitro. Viruses [Internet]. 2020 Dec 5;12(12):1394. Available from: https://pubmed.ncbi.nlm.nih.gov/33291455

69. Ucciferri C, Auricchio A, Di Nicola M, Potere N, Abbate A, Cipollone F, et al. Canakinumab in a subgroup of patients with COVID-19. Lancet Rheumatol [Internet]. 2020 Aug 1;2(8):e457-ee458. Available from: https://doi.org/10.1016/S2665-9913(20)30167-3

70. Razmi M, Hashemi F, Gheytanchi E, Dehghan Manshadi M, Ghods R, Madjd Z. Immunomodulatory-based therapy as a potential promising treatment strategy against severe COVID-19 patients: A systematic review. Vol. 88, International Immunopharmacology. 2020.

71. Chen Y, Wang G, Ouyang L. Promising inhibitors targeting Mpro: an ideal strategy for anti-SARS-CoV-2 drug discovery. Signal Transduct Target Ther [Internet]. 2020;5(1):173. Available from: https://doi.org/10.1038/s41392-020-00291-8

72. Zumla A, Chan JFW, Azhar EI, Hui DSC, Yuen K-Y. Coronaviruses — drug discovery and therapeutic options. Nat Rev Drug Discov [Internet]. 2016;15(5):327–47. Available from: https://doi.org/10.1038/nrd.2015.37

73. V'kovski P, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. Nat Rev Microbiol [Internet]. 2020; Available from: https://doi.org/10.1038/s41579-020-00468-6

74. Dai W, Zhang B, Jiang X-M, Su H, Li J, Zhao Y, et al. Structure-based design of antiviral

drug candidates targeting the SARS-CoV-2 main protease. Science (80-) [Internet]. 2020 Jun 19;368(6497):1331 LP – 1335. Available from: http://science.sciencemag.org/content/368/6497/1331.abstract

75. Zhang L, Lin D, Sun X, Curth U, Drosten C, Sauerhering L, et al. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. Science (80-) [Internet]. 2020 Apr 24;368(6489):409 LP – 412. Available from: http://science.sciencemag.org/content/368/6489/409.abstract

76. Ngo ST, Quynh Anh Pham N, Thi Le L, Pham D-H, Vu V V. Computational Determination of Potential Inhibitors of SARS-CoV-2 Main Protease. J Chem Inf Model [Internet]. 2020 Dec 28;60(12):5771–80. Available from: https://doi.org/10.1021/acs.jcim.0c00491

77. Chhetri A, Chettri S, Rai P, Mishra DK, Sinha B, Brahman D. Synthesis, characterization and computational study on potential inhibitory action of novel azo imidazole derivatives against COVID-19 main protease (M(pro): 6LU7). J Mol Struct. 2021 Feb;1225:129230.

78. Rut W, Lv Z, Zmudzinski M, Patchett S, Nayak D, Snipas SJ, et al. Activity profiling and crystal structures of inhibitor-bound SARS-CoV-2 papain-like protease: A framework for anti–COVID-19 drug design. Sci Adv [Internet]. 2020 Oct 1;6(42):eabd4596. Available from: http://advances.sciencemag.org/content/6/42/eabd4596.abstract

79. Loucera C, Esteban-Medina M, Rian K, Falco MM, Dopazo J, Peña-Chilet M. Drug repurposing for COVID-19 using machine learning and mechanistic models of signal transduction circuits related to SARS-CoV-2 infection. Signal Transduct Target Ther [Internet]. 2020;5(1):290. Available from: https://doi.org/10.1038/s41392-020-00417-y

80. Zhou Y, Wang F, Tang J, Nussinov R, Cheng F. Artificial intelligence in COVID-19 drug repurposing. Lancet Digit Heal [Internet]. 2020 Dec 1;2(12):e667–76. Available from: https://doi.org/10.1016/S2589-7500(20)30192-8

81. Empey KM, Peebles Jr RS, Kolls JK. Pharmacologic advances in the treatment and prevention of respiratory syncytial virus. Clin Infect Dis [Internet]. 2010 May 1;50(9):1258–67. Available from: https://pubmed.ncbi.nlm.nih.gov/20235830

82. Yang L, Liu W, Yu X, Wu M, Reichert JM, Ho M. COVID-19 antibody therapeutics tracker: a global online database of antibody therapeutics for the prevention and treatment of COVID-19. Antib Ther [Internet]. 2020 Feb 18;3(3):205–12. Available from: https://doi.org/10.1093/abt/tbaa020

83. Jones BE, Brown-Augsburger PL, Corbett KS, Westendorf K, Davies J, Cujec TP, et al. LY-CoV555, a rapidly isolated potent neutralizing antibody, provides protection in a non-human primate model of SARS-CoV-2 infection. bioRxiv [Internet]. 2020 Jan 1;2020.09.30.318972. Available from: http://biorxiv.org/content/early/2020/10/09/2020.09.30.318972.abstract

84. Baum A, Fulton BO, Wloga E, Copin R, Pascal KE, Russo V, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science (80-) [Internet]. 2020 Aug 21;369(6506):1014 LP – 1018. Available from: http://science.sciencemag.org/content/369/6506/1014.abstract

85. Baum A, Ajithdoss D, Copin R, Zhou A, Lanza K, Negron N, et al. REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. Science (80-) [Internet]. 2020 Nov 27;370(6520):1110 LP – 1115. Available from:

http://science.sciencemag.org/content/370/6520/1110.abstract

86. Wilt TJ, Kaka AS, MacDonald R, Greer N, Obley A, Duan-Porter W. Remdesivir for Adults With COVID-19 : A Living Systematic Review for an American College of Physicians Practice Points. Ann Intern Med. 2020;

87. Jiang Y, Chen D, Cai D, Yi Y, Jiang S. Effectiveness of remdesivir for the treatment of hospitalized COVID-19 persons: A network meta-analysis. J Med Virol. 2020;

88. Siemieniuk RAC, Bartoszko JJ, Ge L, Zeraatkar D, Izcovich A, Pardo-Hernandez H, et al. Drug treatments for covid-19: Living systematic review and network meta-Analysis. BMJ. 2020;370.

89. Munir MA, Kuganda H, Basry A. The efficacy and safety of antivirus drugs for COVID-19: A systematic review. Vol. 11, Systematic Reviews in Pharmacy. 2020.

90. Bai YX, Xu YH, Wang X, Sun C, Guo Y, Qiu S, et al. Advances in SARS-CoV-2: A systematic review. Vol. 24, European Review for Medical and Pharmacological Sciences. 2020.

91. Wang M, Wu T, Zuo Z, You Y, Yang X, Pan L, et al. Evaluation of current medical approaches for COVID-19: a systematic review and meta-analysis. BMJ Support Palliat Care. 2020;

92. Baroutjian A, Sanchez C, Boneva D, McKenney M, Elkbuli A. SARS-CoV-2 pharmacologic therapies and their safety/effectiveness according to level of evidence. American Journal of Emergency Medicine. 2020.

93. Patel RS, Patel N, Baksh M, Zaidi A, Patel J. Clinical Perspective on 2019 Novel Coronavirus Pneumonia: A Systematic Review of Published Case Reports. Cureus. 2020;

94. Talaie H, Hosseini SM, Nazari M, Fakhri Y, Mousavizadeh A, Vatanpour H, et al. Is there any potential management against COVID-19? A systematic review and meta-analysis. Daru. 2020 Aug;1–13.

95. Kotecha P, Light A, Checcucci E, Amparore D, Fiori C, Porpiglia F, et al. Repurposing of drugs for Covid-19: a systematic review and meta-analysis. Panminerva Med. 2020 Oct;

96. Thoguluva Chandrasekar V, Venkatesalu B, Patel HK, Spadaccini M, Manteuffel J, Ramesh M. Systematic review and meta-analysis of effectiveness of treatment options against SARS-CoV-2 infection. J Med Virol. 2020;

97. Roshanshad A, Kamalipour A, Ashraf MA, Roshanshad R, Jafari S, Nazemi P, et al. The efficacy of remdesivir in coronavirus disease 2019 (COVID-19): a systematic review. Iran J Microbiol [Internet]. 2020 Oct 31;12(5 SE-Review Article(s)). Available from: https://ijm.tums.ac.ir/index.php/ijm/article/view/2695

98. Elsawah HK, Elsokary MA, Abdallah MS, ElShafie AH. Efficacy and safety of remdesivir in hospitalized Covid-19 patients: Systematic review and meta-analysis including network meta-analysis. Rev Med Virol [Internet]. 2020 Oct 31;n/a(n/a):e2187. Available from: https://doi.org/10.1002/rmv.2187

99. Tobaiqy M, Qashqary M, Al-Dahery S, Mujallad A, Hershan AA, Kamal MA, et al. Therapeutic management of patients with COVID-19: a systematic review. Infect Prev Pract. 2020;2(3).

100. Shrestha DB, Budhathoki P, Syed N-I-H, Rawal E, Raut S, Khadka S. Remdesivir: A potential game-changer or just a myth? A systematic review and meta-analysis. Life Sci [Internet]. 2020 Oct 26;118663. Available from:

https://pubmed.ncbi.nlm.nih.gov/33121991

101. Cantini F, Goletti D, Petrone L, Najafi Fard S, Niccoli L, Foti R. Immune Therapy, or Antiviral Therapy, or Both for COVID-19: A Systematic Review. Drugs. 2020.

102. Subramanian K, Nalli A, Senthil V, Jain S, Nayak A, Bhat A. Perspectives on the Early Quality of Evidence Guiding the Therapeutic Management of SARS-CoV-2: A Systematic Literature Review. Vol. 37, Advances in Therapy. 2020.

103. Misra S, Nath M, Hadda V, Vibha D. Efficacy of various treatment modalities for nCOV-2019: A systematic review and meta-analysis. Vol. 50, European Journal of Clinical Investigation. 2020.

104. Juul S, Nielsen EE, Feinberg J, Siddiqui F, Jørgensen CK, Barot E, et al. Interventions for treatment of COVID-19: A living systematic review with meta-analyses and trial sequential analyses (The LIVING Project). PLoS Med. 2020;17(9).

105. Teoh SL, Lim YH, Lai NM, Lee SWH. Directly Acting Antivirals for COVID-19: Where Do We Stand? Front Microbiol. 2020;11.

106. Siordia JA, Bernaba M, Yoshino K, Ulhaque A, Kumar S, Bernaba M, et al. Systematic and Statistical Review of Coronavirus Disease 19 Treatment Trials. SN Compr Clin Med. 2020;2(8).

107. Consortium WST. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. N Engl J Med [Internet]. 2020 Dec 2; Available from: https://doi.org/10.1056/NEJMoa2023184

108. National Institutes of Health. COVID-19 Treatment Guidelines [Internet]. 2020 [cited 2021 Feb 9]. Available from:

https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/

109. Bertsias G. Therapeutic targeting of JAKs: from hematology to rheumatology and from the first to the second generation of JAK inhibitors. Mediterr J Rheumatol [Internet]. 2020 May 25;31(Suppl 1):105–11. Available from: https://pubmed.ncbi.nlm.nih.gov/32676568

110. Portsmore S, Tran Nguyen TN, Beacham E, Neelakantan P. Combined IL-6 and JAK/STAT inhibition therapy in COVID-19-related sHLH, potential game changer. Br J Haematol [Internet]. 2020 Aug 1;190(4):525–8. Available from: https://doi.org/10.1111/bjh.16966

111. Walz L, Cohen AJ, Rebaza AP, Vanchieri J, Slade MD, Cruz CS Dela, et al. JAK-Inhibitor and Type I Interferon Ability to Produce Favorable Clinical Outcomes in COVID-19 Patients: A Systematic Review and Meta-Analysis. Res Sq. 2020;

112. Campbell CM, Guha A, Haque T, Neilan TG, Addison D. Repurposing Immunomodulatory Therapies against Coronavirus Disease 2019 (COVID-19) in the Era of Cardiac Vigilance: A Systematic Review. J Clin Med. 2020;9(9).

113. National Institutes of Health. The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of Baricitinib for the Treatment of COVID-19 [Internet]. 2020 [cited 2021 Feb 9]. Available from: https://files.covid19treatmentguidelines.nih.gov/guidelines/section/section_105.pdf

114. National Institutes of Health. Therapeutic Management of Patients with COVID-19 [Internet]. 2020 [cited 2021 Feb 10]. Available from: https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/

115. Yousefifard M, Mohamed Ali K, Aghaei A, Zali A, Madani Neishaboori A, Zarghi A, et

al. Corticosteroids on the management of coronavirus disease 2019 (Covid-19): A systemic review and meta-analysis. Vol. 49, Iranian Journal of Public Health. 2020.

116. Lu S, Zhou Q, Huang L, Shi Q, Zhao S, Wang Z, et al. Effectiveness and Safety of Glucocorticoids to Treat COVID-19: A Rapid Review and Meta-Analysis. Ann Transl Med. 2020;8(10).

117. Cheng W, Li Y, Cui L, Chen Y, Shan S, Xiao D, et al. Efficacy and Safety of Corticosteroid Treatment in Patients With COVID-19: A Systematic Review and Meta-Analysis. Vol. 11, Frontiers in Pharmacology. 2020.

118. Ye Z, Wang Y, Colunga-Lozano LE, Prasad M, Tangamornsuksan W, Rochwerg B, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. CMAJ. 2020;192(27).

119. Lee KH, Yoon S, Jeong GH, Kim JY, Han YJ, Hong SH, et al. Efficacy of Corticosteroids in Patients with SARS, MERS and COVID-19: A Systematic Review and Meta-Analysis. J Clin Med. 2020;9(8).

120. Li H, Chen C, Hu F, Wang J, Zhao Q, Gale RP, et al. Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis. Vol. 34, Leukemia. 2020.

121. Cano EJ, Fuentes XF, Campioli CC, O'Horo JC, Saleh OA, Odeyemi Y, et al. "Impact of Corticosteroids in COVID-19 Outcomes: Systematic Review and Meta-Analysis." Chest [Internet]. 2020 Oct 28;S0012-3692(20)35107-2. Available from:

https://pubmed.ncbi.nlm.nih.gov/33129791

122. Halpin DMG, Singh D, Hadfield RM. Inhaled corticosteroids and COVID-19: A systematic review and clinical perspective. Vol. 55, European Respiratory Journal. 2020.

123. Zhang JJY, Lee KS, Ang LW, Leo YS, Young BE. Risk Factors for Severe Disease and Efficacy of Treatment in Patients Infected With COVID-19: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis. Clin Infect Dis. 2020;

124. Singh AK, Majumdar S, Singh R, Misra A. Role of corticosteroid in the management of COVID-19: A systemic review and a Clinician's perspective. Diabetes Metab Syndr Clin Res Rev. 2020;14(5).

125. Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. Vol. 81, Journal of Infection. 2020.

126. Sterne JAC, Murthy S, Diaz J V., Slutsky AS, Villar J, Angus DC, et al. Association between Administration of Systemic Corticosteroids and Mortality among Critically Ill Patients with COVID-19: A Meta-analysis. JAMA - J Am Med Assoc. 2020;324(13).

127. Tlayjeh H, Mhish OH, Enani MA, Alruwaili A, Tleyjeh R, Thalib L, et al. Association of corticosteroids use and outcomes in COVID-19 patients: A systematic review and meta-analysis. J Infect Public Health. 2020;

128. Budhathoki P, Shrestha DB, Rawal E, Khadka S. Corticosteroids in COVID-19: Is it Rational? A Systematic Review and Meta-Analysis. SN Compr Clin Med. 2020 Oct;1–21.

129. EMA. Assessment Report - Dexamethasone in hospitalised patients with COVID-19 [Internet]. 2020. Available from:

https://www.ema.europa.eu/en/documents/other/dexamethasone-covid19-article-53-procedure-assessment-report_en.pdf

130. Rajendran K, Krishnasamy N, Rangarajan J, Rathinam J, Natarajan M, Ramachandran A. Convalescent plasma transfusion for the treatment of COVID-19: Systematic review. Vol. 92, Journal of Medical Virology. 2020.

131. Devasenapathy N, Ye Z, Loeb M, Fang F, Najafabadi BT, Xiao Y, et al. Efficacy and safety of convalescent plasma for severe COVID-19 based on evidence in other severe respiratory viral infections: a systematic review and meta-analysis. CMAJ. 2020;192(27).

132. Mansourabadi AH, Sadeghalvad M, Mohammadi-Motlagh HR, Rezaei N. The immune system as a target for therapy of SARS-CoV-2: A systematic review of the current immunotherapies for COVID-19. Vol. 258, Life Sciences. 2020.

133. Sun M, Xu Y, He H, Zhang L, Wang X, Qiu Q, et al. A potentially effective treatment for COVID-19: A systematic review and meta-analysis of convalescent plasma therapy in treating severe infectious disease. Vol. 98, International Journal of Infectious Diseases. 2020.

134. Sarkar S, Soni KD, Khanna P. Convalescent plasma is a clutch at straws in COVID-19 management! A systematic review and meta-analysis. J Med Virol. 2020;

135. Piechotta V, Chai KL, Valk SJ, Doree C, Monsef I, Wood EM, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Vol. 2020, Cochrane Database of Systematic Reviews. 2020.

136. Bakhtawar N, Usman M, Khan MMU. Convalescent Plasma Therapy and Its Effects On COVID-19 Patient Outcomes: A Systematic Review of Current Literature. Cureus. 2020;

137. U.S. Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibody for Treatment of COVID-19 [Internet]. 2020 [cited 2021 Feb 9]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19

138. Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med [Internet]. 2020 Oct 28;384(3):229–37. Available from: https://doi.org/10.1056/NEJMoa2029849

139. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, et al. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA [Internet]. 2021 Jan 21; Available from: https://doi.org/10.1001/jama.2021.0202

140. Eli Lilly and Company. Lilly's bamlanivimab (LY-CoV555) administered with etesevimab (LY-CoV016) receives FDA emergency use authorization for COVID-19 [Internet]. 2021 [cited 2021 Feb 12]. Available from: https://investor.lilly.com/news-releases/news-release-details/lillys-bamlanivimab-ly-cov555-administered-etesevimab-ly-cov016

141. CISION PR Newswire. Lilly's neutralizing antibody bamlanivimab (LY-CoV555) prevented COVID-19 at nursing homes in the BLAZE-2 trial, reducing risk by up to 80 percent for residents [Internet]. 2021 [cited 2021 Feb 10]. Available from: https://www.prnewswire.com/news-releases/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-prevented-covid-19-at-nursing-homes-in-the-blaze-2-trial-reducing-risk-by-up-

to-80-percent-for-residents-301212159.html

142. U.S. Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibodies for Treatment of COVID-19 [Internet]. 2020 [cited 2021 Feb 9]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19

143. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med [Internet]. 2020 Dec 17;384(3):238–51. Available from: https://doi.org/10.1056/NEJMoa2035002

144. Yu Y, Shi Q, Zheng P, Gao L, Li H, Tao P, et al. Assessment of the quality of systematic reviews on COVID-19: A comparative study of previous coronavirus outbreaks. J Med Virol. 2020 Jul;92(7):883–90.

145. Callaway E. The coronavirus is mutating - does it matter? Vol. 585, Nature. England; 2020. p. 174–7.

146. Li Q, Wu J, Nie J, Zhang L, Hao H, Liu S, et al. The Impact of Mutations in SARS-CoV-2 Spike on Viral Infectivity and Antigenicity. Cell [Internet]. 2020/07/17. 2020 Sep 3;182(5):1284-1294.e9. Available from: https://pubmed.ncbi.nlm.nih.gov/32730807

147. Centers for Disease Control and Prevention. Emerging SARS-CoV-2 Variants [Internet]. 2020 [cited 2021 Feb 10]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html

148. Lauring AS, Hodcroft EB. Genetic Variants of SARS-CoV-2—What Do They Mean? JAMA [Internet]. 2021 Jan 6; Available from: https://doi.org/10.1001/jama.2020.27124

149. Moore JP, Offit PA. SARS-CoV-2 Vaccines and the Growing Threat of Viral Variants.

JAMA [Internet]. 2021 Jan 28; Available from: https://doi.org/10.1001/jama.2021.1114

150. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Lambson BE, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. bioRxiv [Internet]. 2021 Jan 1;2021.01.18.427166. Available from: http://biorxiv.org/content/early/2021/01/19/2021.01.18.427166.abstract

151. Eli Lilly and Company. Lilly, Vir Biotechnology and GSK announce first patient dosed in expanded BLAZE-4 trial evaluating bamlanivimab (LY-CoV555) with VIR-7831 (GSK4182136) for COVID-19 [Internet]. 2021 [cited 2021 Feb 11]. Available from: https://investor.lilly.com/news-releases/news-release-details/lilly-vir-biotechnology-and-gsk-announce-first-patient-dosed

152. Pfizer Inc. PFIZER AND BIONTECH ANNOUNCE VACCINE CANDIDATE AGAINST COVID-19 ACHIEVED SUCCESS IN FIRST INTERIM ANALYSIS FROM PHASE 3 STUDY [Internet]. 2020 [cited 2021 Feb 11]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against

153. Moderna Inc. Moderna Announces Primary Efficacy Analysis in Phase 3 COVE Study for Its COVID-19 Vaccine Candidate and Filing Today with U.S. FDA for Emergency Use Authorization [Internet]. 2020 [cited 2021 Feb 11]. Available from: https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-primary-efficacy-analysis-phase-3-cove-study

154. Garde D, Saltzman J. The story of mRNA: How a once-dismissed idea became a leading technology in the Covid vaccine race [Internet]. 2020 [cited 2021 Feb 10]. Available

from: https://www.statnews.com/2020/11/10/the-story-of-mrna-how-a-once-dismissed-idea-became-a-leading-technology-in-the-covid-vaccine-race/

155. The Economist. Israel's vaccine programme gives hope to the world [Internet]. 2021 [cited 2021 Feb 11]. Available from: https://www.economist.com/graphic-detail/2021/02/03/israels-vaccine-programme-gives-hope-to-the-world

156. Perrone F, Piccirillo MC, Ascierto PA, Salvarani C, Parrella R, Marata AM, et al. Tocilizumab for patients with COVID-19 pneumonia. The single-arm TOCIVID-19 prospective trial. J Transl Med [Internet]. 2020;18(1):405. Available from: https://doi.org/10.1186/s12967-020-02573-9

157. Gokhale Y, Mehta R, Karnik N, Kulkarni U, Gokhale S. Tocilizumab improves survival in patients with persistent hypoxia in severe COVID-19 pneumonia. EClinicalMedicine [Internet]. 2020 Jul 1;24. Available from: https://doi.org/10.1016/j.eclinm.2020.100467

158. Somers EC, Eschenauer GA, Troost JP, Golob JL, Gandhi TN, Wang L, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. medRxiv Prepr Serv Heal Sci [Internet]. 2020 Jun 3;2020.05.29.20117358. Available from: https://pubmed.ncbi.nlm.nih.gov/32577684

159. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med [Internet]. 2020 Dec 17;384(1):20–30. Available from: https://doi.org/10.1056/NEJMoa2030340

160. Holt GE, Batra M, Murthi M, Kambali S, Santos K, Bastidas MVP, et al. Lack of tocilizumab effect on mortality in COVID19 patients. Sci Rep [Internet]. 2020;10(1):17100. Available from: https://doi.org/10.1038/s41598-020-74328-x

161. Tsai A, Diawara O, Nahass RG, Brunetti L. Impact of tocilizumab administration on mortality in severe COVID-19. Sci Rep [Internet]. 2020;10(1):19131. Available from: https://doi.org/10.1038/s41598-020-76187-y

162. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Final Report. N Engl J Med [Internet]. 2020 May 22;383(19):1813–26. Available from: https://doi.org/10.1056/NEJMoa2007764

163. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ [Internet]. 2009;339. Available from: https://www.bmj.com/content/339/bmj.b2700