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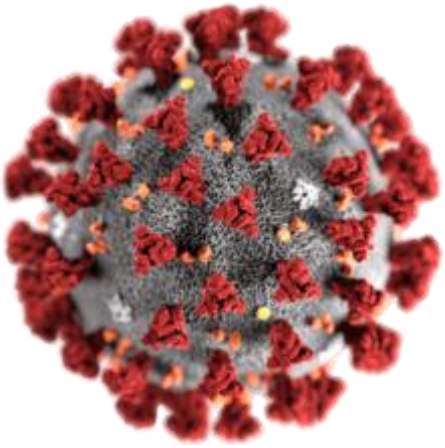

COVID-19 Science Report: Therapeutics

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Announcement

We started the first of our COVID-19 Science Reports in the last week of January 2020, as the very first wave of the COVID-19 pandemic reached Singapore. It was a rapid scan for the current state of development of diagnostics, therapeutics and vaccines that could be useful against the novel coronavirus, as it was called then. It was an urgent request made on a Monday night, and we managed to deliver by that week Friday afternoon.

Since then, it has been a weekly saga (some might call it a nightmare), as we continued to scan and update these reports (highlighting the updated text and paragraphs each week) and added more chapters, first on symptoms and signs, then on laboratory and imaging findings, and then on containment measures. Each addition was responding to yet another urgent request and delivered in the same three to four days, and subsequently updated each week as we continued our scans.

By the fifth week, the Science Report had grown to well over a hundred pages (not counting of course the references) and had become somewhat unwieldy. This was also the same time we were requested to make the report available for downloading on the School's website. We broke up the report into five stand-alone Science Reports and launched them online on 28 February. We were pleasantly surprised by its reception. What started off as "national service" to support our local healthcare and government sector was praised, shared, and even tweeted about.

As the pandemic progressed, we did other reports as well, of course, for the government and for other agencies, not all of which made it online for various reasons. We summarised the available data on fomite-mediated transmission, the risks and management of persons in high density accommodations, how different countries are moving into lockdowns, the use of digital technologies in containment, business continuity measures for enterprises, stay home strategies, and more.

Through it all, our small team were able to deliver on time each week, working through weekends, juggling pieces of work in progress and helped by a group of enthusiastic and hardworking medical students and Public Health interns (some of whom were volunteering their vacations to help). It's been 19 weeks since we started the Science Reports and it is a good time to review and consolidate.

There are now many repositories that cover much of the same ground as our clinical characteristics, diagnostics, therapeutics and vaccines reports. There is also a lot more known about these aspects as clinicians around the world treat their patients. Our student interns have to move on as well, some to examinations, others back to their courses. We will therefore freeze our reports on 1 June 2020, enabling us to focus on the ones that continue to be of critical importance in the global and national responses to COVID-19.

For continuing information on **therapeutics** and vaccines of COVID-19, please see:

- **UK NICE**. *Rapid review evidence summaries and guidance to support clinical practice.*
- **WHO Clinical management interim guidance V1.2**
- **CDC Interim Clinical Guidance**
- Clinical Trial Registries: **US** & **China**. *Latest clinical trials for therapeutics, treatment and vaccines.*
- **WHO Coronavirus disease (COVID-2019) R&D.** *Latest WHO information on therapeutics and vaccines.*
- **WHO draft landscape of COVID-19 candidate vaccines.** *Regularly updated table of the key vaccine candidates and their level of development.*
- **Milken Institute Treatment and Vaccine Tracker.** *Aggregation of publicly-available information from validated sources on vaccines and therapeutics in development.*

Contents

Therapeutics

The following report summarises the latest findings in relation to therapeutics for treatment of COVID-19 and the clinical trials in progress. This is not a clinical guideline and does not make recommendations. Some references were from preprints which are preliminary and yet to be peer reviewed, the results should be interpreted with caution.

Introduction

There is currently no evidence from randomised control trials to support specific drug treatment against COVID-19 in suspected or confirmed cases. The optimal selection of anti-viral agents and interventions targeting the virus is not yet known. Many different treatments are being used in clinical trials and via compassionate use protocols.

The WHO together with stakeholders has developed and published a Global Research Roadmap for COVID-19. Therapeutics is a key priority area.[1] The Roadmap sets out the key activities and the expected timeline.

Wellcome, Bill & Melinda Gates Foundation and Mastercard Impact Fund have set up the COVID-19 Therapeutics Accelerator. Working with the WHO, government and private sector funders and organisations, as well as the global regulatory and policy-setting institutions, the Accelerator will have an end-to-end focus, from drug pipeline development through manufacturing and scale-up. A key aim is for equitable access, including treatment availability and affordability in low-resource settings.[2]

Learning from SARS and MERS

The SARS-CoV and MERS-CoV were coronavirus outbreaks that occurred in 2003 and 2012 respectively. However, there has been no global consensus on gold standard therapy, although much research has been undertaken. Given that SARS-CoV-2 is from the coronavirus family as well and has proven similarities to SARS-CoV in terms of viral morphology (eg their spike protein ACE2), much research has been undertaken to consider SARS-CoV and MERS-CoV drugs in the fight against COVID-19.[3]

Repurposing Drugs

Developing and obtaining regulatory approval for new drugs can take years. Since the emergence of COVID-19, scientists have been working to identify key target sites on the virus for drug treatment and scanning existing drugs to determine if any may be potential candidates to effectively treat COVID-19 infections. Existing drugs have the benefit of already being approved as safe for human use and have established manufacturing arrangements.

More is now known regarding the structure of the virus and this has enabled screening for repurposed drugs to test for effectiveness against COVID-19.[4,5,6] Previous research on coronaviruses has also been utilised.[7] Potential candidates need to be experimentally tested in cell culture and through clinical trials.

One critical action is finding a suitable animal model to test potential therapeutics (as well as vaccines). Finding a suitable animal model has been a challenge.[8] Research has suggested that ferrets could be a possible animal model candidate as the virus replicates efficiently in their upper respiratory tract.[9]

WHO has published a scientific brief on off-label use of medications for COVID-19.[10]

Clinical Trials

Numerous clinical trials have commenced based on possible treatment candidates. Lists of the clinical trials can be found at the following:

- US Clinical Trial Registry
- Chinese Clinical Trial Registry
- WHO hosts a web base application to analyse clinical trials to evaluate therapeutics for COVID-19

The UK has launched the RECOVERY trial.[11] The trial is supported by a grant to the University of Oxford from UK Research and Innovation/National Institute for Health Research (NIHR) and by core funding provided by NIHR Oxford Biomedical Research Centre, Wellcome, the Bill and Melinda Gates Foundation, the Department for International Development, Health Data Research UK, the Medical Research Council Population Health Research Unit, and NIHR Clinical Trials Unit Support Funding. The RECOVERY Trial will begin by testing some of these suggested treatments:

- Lopinavir-Ritonavir
- Low-dose Dexamethasone
- Hydroxychloroquine
- Azithromycin
- Tocilizumab

Data from the trial will be regularly reviewed so that any effective treatment can be identified quickly and made available to all patients. The RECOVERY Trial team will constantly review information on new drugs and include promising ones in the trial. Tocilizumab will be used for patients whose clinical status worsened after being enrolled in the trial. [12]

A recent review of the Chinese Clinical Trial Registry identified over a hundred clinical studies of new coronavirus infection, including antiviral drugs, antimalarial drugs, glucocorticoids, plasma therapy, virus vaccine and other medications. Traditional Chinese Medicine accounted for half of studies. There is concern that the multiple trials have been instigated rapidly and the basis and design of some may be questionable. A study reviewing clinical trials concluded that caution is needed in regard to reducing potential risk to patients in clinical trials, and the interpretation of results.[13]

Although many clinical trials have been registered in China, a systematic review posted on 17 March 2020 which has yet to be peer-reviewed found that only 11 trials have begun to recruit patients, and most were in early clinical exploratory trials or in pre-experiment stage (only two trials of remdesivir in phase III), and the sample size of subjects recruited is small (Median 100 days, IQR 60–200). The median duration of trials was 179 days (IQR 94–366). Overall, both the methodology quality of intervention register trials and observational trials are low.[14] Another review of clinical trials concluded that outcome reporting is inconsistent.[15]

Another review of clinical trials has also been undertaken, highlighting the main treatments under study (in order of number of clinical trials - stem cells therapy, lopinavir/ritonavir, chloroquine, umifenovir, hydroxychloroquine, plasma treatment, favipiravir, methylprednisolone, and remdesivir.[16]

WHO has launched a large global trial programme, called SOLIDARITY, this involves multiarm, multicountry clinical trials for potential coronavirus therapies, part of an aggressive

effort to jumpstart the global search for drugs to treat COVID-19. The trials have been designed to be as simple as possible so that even hospitals overwhelmed by COVID-19 patients can participate.

The drugs to be tested are the antiviral drug remdesivir; a combination of two HIV drugs, lopinavir and ritonavir; lopinavir and ritonavir plus interferon beta; and the antimalarial drug chloroquine. Some countries will test chloroquine against the standard of care while others will test hydroxychloroquine, a related drug.[17]

Clinical Guidelines / Standardised Treatment Protocol

WHO regularly updates its interim clinical management guidelines for COVID-19.[18] Some countries have created clinical guidelines which map back to these.[19]

CDC regularly updates its Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). The CDC has also released guidelines for management of paediatric patients on 15 May 2020 and of neonates at risk for COVID-19 on 20 May 2020. [20]

NICE (UK National Institute for Health and Care Excellence) has published COVID-19 rapid guidelines covering COVID-19 and areas ranging from critical care in adults to delivery of radiotherapy. [21] As of 19th May 2020, they have updated their categorisation of guidelines into the following:

Grouping	Content
Managing Symptoms and complications	• Acute myocardial injury • Antibiotics for pneumonia in adults in hospital • Critical care in adults • Managing suspected or confirmed pneumonia in adults in the community • Managing symptoms (including at the end of life) in the community • Acute kidney injury in hospital
Managing conditions that increase risk	• Children and young adults who are immunocompromised • Community-based care of patients with chronic obstructive pulmonary disease • Cystic fibrosis • Dermatological conditions treated with drugs affecting the immune response • Gastrointestinal and liver conditions treated with drugs affecting the immune response • Rheumatological, autoimmune, inflammatory and metabolic bone disorders • Severe asthma • Chronic Kidney disease

	• Interstitial Lung disease
Providing services during the pandemic	• Delivery of radiotherapy • Delivery of systemic anticancer treatments • Haematopoietic stem cell transplantation • Dialysis service delivery

Following publication of the critical care guideline NICE received concerns from patient groups regarding the application to people with learning disabilities, autism and other stable long-term disabilities. The NHS Specialist Clinical Frailty Network updated their advice on using the frailty score, stating that it should not be used in isolation to direct clinical decision making and that clinicians should take any decisions about care in conjunction with patients and their carers where possible. The new advice also includes a clarification that the tool should not be used in certain groups, including those with learning disabilities or with stable long-term disabilities such as cerebral palsy. NICE has now (25 March) updated the rapid COVID-19 critical care guideline to reflect these clarifications and to emphasise the need to consider additional patient factors when interpreting the frailty score.[22]

NICE is undertaking rapid evidence reviews to look at whether certain medicines may increase the severity or length of COVID-19 illness. NICE is currently reviewing ibuprofen and other non-steroidal anti-inflammatory drugs used to reduce temperature and ease flu-like symptoms. Paracetamol was suggested to be used in preference to NSAIDs, though patients on long term NSAIDs for other comorbidities should not withhold their medication. [23]

It is also reviewing angiotensin converting enzyme (ACE) inhibitors used to treat high blood pressure or heart failure. NICE are working with the Medicines and Healthcare products Regulatory Agency to facilitate rapid review of information and advice on the safety and efficacy of treatments for COVID-19.

National Institutes of Health (NIH) in the United States has published treatment guidelines. [24] The guidelines include:

1) Therapeutics - antivirals and immunotherapies
2) Optimal management of patients at various stages of infection via stratification of patients by their risk of infection and severity of disease. These include pregnant women and children.
3) Recommendations for critically ill patients
4) Recommendations with regards to use of concomitant medications (statins, corticosteroids, NSAIDs, ACE-I and ARBs)

Cochrane has made available Special Collections on COVID-19. One on evidence relevant to critical care and one on infection control and prevention measures. The critical care collection includes Cochrane Reviews on the following topics: fluid and vasopressor therapy; respiratory support and mechanical ventilation; weaning mechanical ventilation; managing hypoxaemia; pharmacological treatment; and nutrition in intensive care.[25]

Lancet has published correspondence on therapeutic options for severe acute respiratory distress syndrome and ECMO related to coronavirus disease 2019.[26,27]

The Lancet has also published guidance on the management of COVID-19 patients in intensive care.[28]

British Medical Journal (BMJ) provides a set of treatment algorithms, including both suspected and confirmed COVID-19 cases. [29]

Countries

Several countries have outlined additional treatments to consider. These are based on the current available evidence (mainly from treatment of SARS, MERS and early cases of COVID-19) and clinical consensus. Robust evidence specific to the treatment of COVID-19 has yet to be published. Guidance are subject to ongoing review and adaptation.

- **China** has published a rapid advice guideline for the diagnosis and treatment of 2019 novel infected pneumonia.[30] The National Health Commission of the People's Republic of China has also issued treatment guidelines.[31]
- **South Korea** has developed treatment guidelines.[32]
- **Singapore** has interim treatment guidelines for COVID-19.[33]
- **America.** The Infectious Diseases Society of America has published guidelines on the treatment and management of patients with COVID-19.[34] Interim guidance has also been published from the American Thoracic Society, which led an international task force to review the evidence to date.[35] Yale Medicine has also developed and published a treatment algorithm.[36]

Main Therapeutics

The main therapeutics we will report in this section are:

1) **Remdesivir**
2) **Lopinavir/Ritonavir**
3) **Interferons**
4) **Chloroquine or Hydroxychloroquine**
5) **Hydroxychloroquine with Azithromycin**

WHO has collated the latest reports on COVID-19 therapeutics and trials. The following section should be read alongside the WHO collation. As well as the clinical trials registries:

US Clinical Trial Registry and the Chinese Clinical Trial Registry.

As outlined above, the WHO is sponsoring clinical trials for remdesivir; lopinavir/ritonavir; lopinavir/ritonavir plus interferon beta; and the antimalarial drug chloroquine. Some countries will test chloroquine against the standard of care while others will test hydroxychloroquine, a related drug.[37]

Remdesivir

Remdesivir (GS-5734) is an investigational broad-spectrum antiviral agent with in vitro activity against multiple RNA viruses, including Ebola and CoV. It is a nucleotide-analog inhibitor of RNA-dependent RNA polymerases. Made by Gilead, this nucleoside analog is a potential candidate[38,39,40] that shows promise against COVID-19 based on in-vitro studies[41].

Hundreds of patients in have received remdesivir treatment on a compassionate use (otherwise known as expanded access) basis.[42]

Data suggests that timing of antiviral initiation may be important, as “administration of remdesivir with high viral loads seen after peak viral titer failed to reduce lung damage despite reducing viral loads”.[43]

A study[44] done on compassionate use of Remdesivir for 53 patients with severe COVID-19, showing some promising results. By the end of this trial, clinical improvement was observed in 36 of 53 patients (68%). However, a proper measurement of efficacy will require ongoing randomized controlled trials of Remdesivir therapy.

A special announcement[45] by Dr Anthony Fauci on 30 April 2020 from USA revealed that a government funded study found promising results regarding Remdesivir effectiveness in COVID-19 infections. This double-blinded, randomised, placebo-controlled trial was published in the New England Journal of Medicine on 22 May 2020. It found that a 10 day course of Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalised with COVID-19 and evidence of lower respiratory tract infection. [46]

It was also reported on 3 May 2020 that remdesivir has gotten emergency approval in the US for COVID-19. Singapore’s NCID and general public hospitals are jointly participating in 3 global drug trials for remdesivir (1 with NIH and 2 with Gilead). [47]

However, a randomised, double-blinded, placebo-controlled multicentre trial was done in China on remdesivir and was published on 29 April 2020. This study found that remdesivir did not have statistically significant clinical benefits but notes that earlier recorded benefit in reduction time to clinical improvement needed larger studies to confirm. [48]

Lopinavir/Ritonavir with/without Interferons

A systematic review of the evidence related to lopinavir-ritonavir and SARS and MERS[49] suggests it could be a potential treatment for COVID-19 infections.[50] Lopinavir/ritonavir, is an antiviral used to treat HIV/AIDS. It acts as a protease inhibitor that targets viral proteases (3CLpro, otherwise known as Mpro) which control coronavirus replication[51], and is used regularly in the treatment of COVID-19. It is marketed as Kaletra or Aluvia by AbbVie pharmaceuticals. Ritonavir is also produced by Ascletis as a generic.[52]

Singapore has treated patients with Lopinavir/Ritonavir with variable clinical outcomes.[53]

South Korean guidelines suggest “lopinavir 400mg/ritonavir 100mg (Kaletra two tablets, twice a day) or chloroquine 500mg orally per day. There is no evidence that using lopinavir/ritonavir with chloroquine is more effective than monotherapies.” Combining lopinavir/ritonavir with chloroquine or hydroxychloroquine could cause side effects, such as arrhythmia from prolonged QT intervals, and “should be administered cautiously”.[54]

China’s rapid advice guideline suggests considering α-interferon and antivirals Lopinavir/Ritonavir. These recommendations are categorised as “weak” as they are based on low-level evidence from retrospective cohorts, historically controlled studies, case reports, and case series in the treatment of MERS and SARS.[55] There is concern about the potency and effectiveness of HIV protease inhibitors against the 3-chymotrypsin-like and papain-like proteases of SARS-Cov-2, considering that HIV protease inhibitors are optimized to fit C2-symmetric catalytic sites, which are absent in coronavirus proteases.[56]

A study in China included 134 confirmed COVID-19 patients. Of these, 52 received Lopinavir/Ritonavir; 34 received Umifenovir (under the brand name Arbidol) (another antiviral recommended by China’s health authorities) and 48 were not given antivirals. Treatments were for seven days. All patients also received Interferon spray medication. After seven days there was no statistically significant difference in medical outcomes between the three groups.[57]

A Chinese retrospective study of 120 patients suggests that the early administration of Lopinavir/Ritonavir could shorten the duration of viral shedding.[58]

AbbVie has announced plans to evaluate HIV medicine Kaletra / Aluvia (lopinavir / ritonavir) as Covid-19 treatment. The company entered into partnerships with health authorities and institutions in various countries to investigate the efficacy and antiviral activity of the medication. AbbVie donated Aluvia to China in January for experimental use against the new viral disease. According to Chinese media reports, Kaletra / Aluvia is effective against COVID-19. The company adds that it lacks access to Chinese clinical information to confirm the accuracy of these reports.[59]

A recent randomised trial found that lopinavir–ritonavir treatment added to standard supportive care was not associated with clinical improvement or mortality in seriously ill patients with COVID-19 different from that associated with standard care alone. There was an average 1 day difference in the time to clinical improvement (lopinavir–ritonavir 15 days vs. standard treatment 16 days). The percentages of patients with detectable viral RNA at various time points were similar. Lopinavir–ritonavir treatment was stopped early in 13 patients (13.8%) because of adverse events (including anorexia, nausea, abdominal discomfort, or diarrhoea, as well as two serious adverse events, both acute gastritis). However, the numbers of lopinavir–ritonavir recipients who had serious complications (acute kidney injury and secondary infections) or requiring non-invasive or invasive mechanical ventilation for respiratory failure were fewer than in those not receiving treatment. These observations are hypothesis-generating and require additional studies to determine whether lopinavir–ritonavir treatment given at a certain stage of illness can reduce some complications in COVID-19. The trial had several limitations. For example, it was not blinded and the lopinavir–ritonavir group had somewhat higher throat viral loads. Use of concurrent pharmacologic interventions, such as glucocorticoids, could also have been a confounding factor.[60]

A phase 2 trial was done in Hong Kong. A triple combination therapy - lopinavir/ritonavir, interferon 1b and ribavirin, was given to patients with mild to moderate COVID-19. When this combination was given within 7 days of symptom onset, it was shown to be effective in reducing the viral shedding of SARS-CoV-2 compared to lopinavir/ritonavir alone. Majority of the patients had negative PCR specimens by day 8. Triple therapy could be more effective than the use of lopinavir/ritonavir alone. [61]

Interferon (IFN)

Interferons are a group of several related proteins that are produced by the body's cells as a defensive response to viruses. They are important modulators of the immune response.[62] Interferon nebulization or sprays (in particular interferon-α) have been shown to reduce viral load in the early stage of infection in conditions such as viral pneumonia, acute URTIs, hand foot mouth disease, and SARS. Early administration leads to shortening duration of disease and decreasing severity of symptoms. Interferons have been used by many clinicians in the treatment of COVID-19 infection, but its efficacy still remains to be determined.[63,64]

One of the ongoing clinical trials involves a recombinant IFN- α, Novaferon.[65]

A retrospective study[66] (pre-print) done in Wuhan, China demonstrated the effectiveness of nebulised interferon-a2b. Regardless of whether it was administered with or without arbidol. There was reduction in the duration which the virus was detected in the respiratory tract and which inflammatory markers were elevated.

Synairgen, a pharmaceutical company based in the UK, is beginning trials on SNG001, an inhaled form of interferon-β-1a. SNG001 was the only inhaled therapy recognised by WHO's

Landscape analysis of therapeutics. During the MERS outbreak, Synairgen conducted a study with NIH in the US and proved that SNG001 had a protective effect against MERS-CoV infection in vitro. [67]

Chloroquine

In vitro studies found that chloroquine was effective in blocking COVID-19 infection at low-micromolar concentration. Based on the treatment of 100 patients with chloroquine the drug has been recommended for inclusion in COVID-19 clinical guidelines in China.[68,69] China published an expert consensus that recommended chloroquine phosphate tablet, 500mg twice per day for 10 days for patients diagnosed as mild, moderate and severe cases of novel coronavirus pneumonia, and without contraindications to chloroquine.[70]

Although traditionally viewed as an antimalarial drug, chloroquine is also recognised as having broad anti-viral properties (against HIV type 1, hepatitis B and HCoV-229E). It is also used as an anti-inflammatory in some conditions (rheumatoid arthritis and lupus erythematosus). Its combined anti-viral and anti-inflammatory actions may account for its potential efficacy in treating patients with COVID-19.[71,72,73,74]

Although there has been son initial hope surrounding the efficacy of Chloroquine, some Swedish hospitals have stopped their usage of chloroquine for COVID-19 patients after reports of severe side effects such as loss of peripheral vision. [75]

Preliminary findings from a randomised, double-blinded, phase IIb clinical trial of chloroquine diphosphate reported that the higher dosage (12g total dose over 10 days) should not be recommended because of safety concerns regarding QTc prolongation and increased lethality. Among patients randomised to the lower dosage group (5 days of treatment, total dose 2.7 g) it is still not possible to determine clear benefit in patients with severe COVID-19 related ARDS. Preliminary data on viral clearance in respiratory secretions are also indicative of little effect of the drug at high dosage.[76]

Hydroxychloroquine

Ongoing randomised clinical trials with hydroxychloroquine should provide a definitive answer regarding the alleged efficacy and will assess its safety.

Hydroxychloroquine, like chloroquine, can lead to severe side effects in patients. Hydroxychloroquine has been known to cause QT interval prolongation and potentially lethal cardiac arrhythmia in certain COVID-19 patients.[77,78]

South Korean guidelines suggest the use of lopinavir/ritonavir or chloroquine orally each day. As chloroquine is not available in Korea, hydroxychloroquine 400mg orally per day has been considered. “There is no evidence that using lopinavir/ritonavir with chloroquine is more effective than monotherapies. Combining lopinavir/ritonavir with chloroquine or hydroxychloroquine could cause serious arrhythmias and drug interactions due to the increased QT interval”. Thus, it has been suggested that these drug combinations should be carefully administered, and only in selected cases.[79]

Hydroxychloroquine was found to be more potent than chloroquine to inhibit SARS-CoV-2 in vitro.[80] At least two RCTs are ongoing for this treatment.[81,82] The University of Groningen has created hydroxychloroquine in aerosol form which could be available shortly, this could be more effective than oral form, although evidence is awaited.[83] A Chinese study of 62 patients, where 31 received a hydroxychloroquine for 5-day at 400 mg, above standard treatment, reported that hydroxychloroquine reduced the time to clinical recovery and

pneumonia improved more in the treatment group.[84] However, this is a small study and larger-scale RCT are ongoing.

Some other studies however, have shown that there is no evidence for use of hydroxychloroquine in hospitalised COVID-19 patients. [85] However, they might alleviate clinical symptoms. [86]

An observational study in the United States has proven that hydroxychloroquine does not significantly improve the clinical outcome for COVID-19 patients. As such, they have excluded the recommendation for hydroxychloroquine use for these patients. [87] Results of observational studies are unable to eliminate the possibility of harmful effects of the drugs being tested, which can only be discovered through well-designed randomised controlled trials. [88] An additional study conducted in China also found no significant improvement in clinical outcomes with the use of hydroxychloroquine. In addition, higher frequency of adverse events were observed in the intervention group receiving hydroxychloroquine. [89]

Another malarial therapeutic, Mefloquine, is being considered in Russia (combined with antibiotic).[90]

On 25 May 2020, the WHO has suspended drug trials on hydroxychloroquine, citing “safety concerns” as the main reason. [91]

Hydroxychloroquine and Azithromycin

A prospective study of 11 patients was undertaken (in France). These patients had received the same regimen outlined in the above study (hydroxychloroquine (600 mg/d for 10 days) and azithromycin (500 mg Day 1 and 250 mg days 2 to 5). The study found no evidence of rapid antiviral clearance or clinical benefit of the combination of hydroxychloroquine and azithromycin for treatment of severe COVID-19.[92]

Hydroxychloroquine and azithromycin are associated with QT prolongation and CDC advises caution is advised when considering these drugs in patients with chronic medical conditions (e.g. renal failure, hepatic disease) or who are receiving medications that might interact to cause arrythmias.[93] Azithromycin alone has also been shown to have possible inhibitory effect on SARS-CoV-2 replication.

Azithromycin alone has also been shown to have possible inhibitory effect on SARS-CoV-2 replication. [94]

Pfizer is planning to publish a review of azithromycin’s in-vitro and clinical data as an antiviral compound. This open-access review is expected to enable the evaluation of azithromycin in future COVID-19 research.[95]

In a study analysing data from 671 hospitals across six continents, the efficacy of hydroxychloroquine with or without a macrolide (which includes Azithromycin) was unable to be confirmed. Use of hydroxychloroquine or chloroquine in drug regimens was associated with a lower in-hospital survival and higher frequency of ventricular arrhythmias while being hospitalised. [96] However, it is important to note that the data on this paper has been called into question. A group of over 140 scientist, researchers and statisticians have published an open letter[97] to the authors of the aforementioned paper (and to the editor of The Lancet), stating their concerns regarding the statistical analysis and data integrity of the study and asking the authors to release the data publicly for the WHO or an independent organisation to analyse. One of the Lancet study investigators said that they will also conduct an independent review of the data. [98]

Fake Cures and Misinformation

There have been numerous reports of fake “cures” and misinformation around experimental treatments for COVID-19. Scammers, internet trolls and even prominent country leaders have spread false information regarding COVID-19, resulting in sometimes fatal consequences.

An investigation by the US State Department found 7% of all coronavirus content on Twitter was false. [99] Facebook, Twitter, Instagram and TikTok have circulated fake cures, such as: garlic, bleach, even cocaine.[100]

Social media platforms, individual governments, and WHO are attempting to combat false information. WHO has used social media platforms such as Twitter, WhatsApp and TikTok to promote credible information. WHO also has a dedicated myth-busting section on their website.[101]

Examples of therapeutic misinformation:

- Methanol – It has been reported that hundreds of Iranians have died or become seriously ill after consuming methanol as it was said to be a “cure” for COVID-19.[102]
- Chloroquine – A US man died and his wife was left in critical condition after they consumed fish tank cleaner which supposedly was marketed to have the “same active ingredient as chloroquine”. Three men in Nigeria also overdosed on chloroquine. These incidents occurred after President Trump repeatedly recommended that the antimalarial drug chloroquine be used as a treatment for COVID-19 despite the lack of evidence.[103] The clinical trial research into chloroquine is ongoing, but for now has been approved by the FDA for emergency treatment only.
- Bleach – A YouTuber tweeted to more than 121,000 followers that the "miracle mineral solution" can destroy COVID-19. This involved drinking bleach.[104]
- Disinfectants in general – President Trump also suggested at a press conference on 24th April 2020 that injecting or ingesting disinfectant could help eliminate the virus in the body, sparking fears that his suggestion could cause harm. He later passed the comment off as “sarcasm”. [105]
- Spraying alcohol and chlorine over skin - WHO have stated that spraying such substances can be harmful to clothes or mucous membranes (i.e. eyes, mouth).[106]
- Cocaine – Social media circulated that cocaine can kill the coronavirus.[107]
- Garlic – Garlic may have some antimicrobial properties, but the WHO has stated there is no evidence from the current outbreak that eating garlic has protected people from the new coronavirus. [108]
- Chlorine dioxide – Social media circulated a claim that a necklace which released chlorine dioxide could prevent COVID-19 infections.[109]

The US Food and Drug Administration and the Federal Trade Commission have warned seven US companies selling fraudulent products that claim to treat or prevent COVID-19. Products included teas, essential oils, tinctures and colloidal silver. The FDA had previously warned that colloidal silver is not safe or effective for treating any disease or condition. Companies that sell products that fraudulently claim to prevent, treat or cure COVID-19 may be subject to legal action, including but not limited to seizure or injunction.[110]

Drug Shortages

Globally, the COVID-19 pandemic has led to shortages of some medications due to factory closures in some countries (China and India), supply chain disruptions, hoarding of medications, and countries banning export of drugs.[111] There are reported shortages of certain medicines, particularly those used for patients with COVID-19. These include medicines used in intensive care units such as some anaesthetics, antibiotics and muscle relaxants as well as medicines used off-label for COVID-19.[112]

Patient groups, representing those who take hydroxychloroquine for lupus and rheumatoid arthritis, have reported shortages. Novartis, Sanofi, Teva and Mylan make hydroxychloroquine and they have stated that they will increase production for compassionate use and under clinical trial. India manufactures hydroxychloroquine; it had stated an export ban, but seems to have altered this position in light of potential US retaliation.[113]

Indonesian HIV patients are currently facing shortages of antiretroviral drugs. As such, the government is looking to purchase tenofovir-based regimens by special arrangements from India. However, this is still insufficient to meet the current shortage faced by the entire country. [114]

Chemoprophylaxis

Chloroquine/Hydroxychloroquine

Hydroxychloroquine is currently under investigation in clinical trials for pre-exposure or post-exposure prophylaxis of SARS-CoV-2 infection, and treatment of patients with mild, moderate, and severe COVID-19. In the United States, several clinical trials of hydroxychloroquine for prophylaxis or treatment of SARS-CoV-2 infection are planned or will be enrolling soon. [115] The implementation of antiviral treatment and prophylaxis has several requirements. The stockpile of drugs must be adequate, the safety of treatment must be very high, and costs should ideally be low. The antimalarial drug, hydroxychloroquine, is licensed for the chemoprophylaxis and treatment of malaria and as a disease modifying antirheumatic drug. It has a history of being safe and well tolerated at typical doses. Multicentre randomised controlled trial will evaluate the efficacy of prophylactic hydroxychloroquine in preventing secondary SARS-CoV-2 infections and disease symptoms among contacts of positive cases.[116]

So far, there has been a lack of clinical guidance for the use of chloroquine for pre or post-exposure prophylaxis due to absence of clinical trials. Similarly, the John Hopkins University JHMI Clinical Guidance for COVID-19 does not recommend any prophylaxis. [117]

A clinical trial was started by the University of Oxford on Chloroquine/hydroxychloroquine for prophylaxis use on 11 March 2020. It is a double-blinded, randomised, placebo-controlled trial that will be conducted in healthcare settings. The last update posted was 27 March 2020.

A pilot project has been launched in Mumbai, India, to trial hydroxychloroquine as prophylaxis. The drug will only be administered for people aged 18 to 55 and without any comorbidities. [118]

Antivirals

A combination of Ribavirin and Lopinavir/Ritonavir has been used as a post-exposure prophylaxis in health care workers who had been exposed to MERS-CoV-infected patients

and demonstrated a reduction in the risk of infection.[119] These have also been used as prophylaxis against SARS-CoV, but were shown to have no difference in clinical outcome compared to standard care alone. [117]

A Chinese retrospective case-control study looked at the potential of Arbidol to be used as a post-exposure prophylaxis. The small study included 27 families and 124 health care workers who had been exposed to patients with confirmed COVID-19 infections. Arbidol was found to reduce the likelihood of developing COVID-19 (Oseltamivir was also studied and not found to be beneficial in preventing infection).[120]

A pre-print meta-analysis on the potential and safety of antiviral agents in Children concluded that there is no evidence showing the effectiveness of antiviral agents for children with COVID-19, and the clinical efficacy of existing antiviral agents is still uncertain. [121]

Interferon

Prophylactic human interferon alpha nasal drops (2-3 drops per nostril, 4 times a day) were suggested to be effective in preventing contraction of COVID-19 among healthcare workers in China with low risk of exposure in a pre-print paper. However, this study was done with all workers being provided with proper protective gear. For healthcare workers with high risk of exposure, nasal drops combined with weekly thymosin alpha subcutaneous injections were proposed as prophylaxis.[122]

Immunotherapies

An antibody, S309, was identified as a human monoclonal antibody with broad neutralising activity against different sarbecoviruses (including SARS-CoV-2 virus) by recognising a highly conserved epitope in the SB domain consisting of N343-glycan. S309 can also recruit effector mechanisms and synergises with weak neutralising monoclonal antibodies, decreasing risk of viral escape. This could be potentially used for prophylaxis for high-risk individuals or for treatment of severe disease. [123]

Drug Treatments Being Considered

More is now known regarding the structure of the virus and this has enabled screening for repurposed drugs to test for effectiveness against COVID-19. Some of these potential candidates are highlighted below. Most of drugs are at an early stage of being explored as potential treatments for COVID-19. The WHO landscape table is a useful document to look through to identify progress of each, as well as others.

Repurposed Antiretroviral (HIV) Drugs

Darunavir/Cobicistat

Janssen Pharmaceutical Companies donated its Prezcobix® HIV medication (darunavir/cobicistat) for use in research activities aimed at finding a treatment for COVID-19.[124] Prezcobix® is currently studied in a trial funded by the Shanghai Public Health Clinical Centre, while Precobix is studied in another Chinese trial.[125]

In-vitro studies have shown that darunavir caused inhibition of SARS-CoV-2 virus in the cell models at a concentration of 300μM. Its inhibition efficacy was 280-fold of that in the untreated group. [126] However, a study has found no in-vitro efficacy of Darunavir/Cobicistat at clinically relevant concentrations.[127,128]

Emtricitabine/Tenofovir

The triphosphates of Emtricitabine and Tenofovir has been shown to act as terminators for the SARS-CoV-2 RdRp catalysed reaction, thus making it a potential drug against COVID-19. [129]

The efficacy of the combination of the non-nucleoside reverse transcriptase inhibitor and nucleotide reverse transcriptase inhibitor, with lopinavir/ritonavir is studied in a clinical trial in Sichuan, China. [130]

Saquinavir

Saquinavir was identified as candidates for COVID-19 therapy based on virtual high throughput screening of clinically approved drugs and the structure of SARS-CoV-2. It is an antiretroviral drug used together with other medications to treat or prevent HIV/AIDS.[131]

Azuvudine

Azuvudine is a nucleoside reverse transcriptase inhibitor that is currently pending a clinical trial for use against COVID-19. [132]

Atazanavir

Atazanavir is an antiretroviral drug of the protease inhibitor class, typically used in the treatment of HIV. Atazanavir has been shown in molecular dynamic analysis to bind more strongly to SARS-CoV-2 Mpro active site than Lopinavir. In-vitro assays with different cell types showed that Atazanavir with or without ritonavir inhibited SARS-CoV-2 replication. Furthermore, Atazanavir performed better than chloroquine in reducing virus-induced IL-6 and TNFα levels. [133]

Repurposed Anti-Influenza Drugs

Favipiravir

Favipiravir, an antiviral (developed by Toyama Chemical, Fujifilm Holdings Corp.) usually used to treat influenza, is being explored as a possible treatment.[134] Favipiravir is a purine nucleoside that acts as competitive inhibitor of viral RNA-dependent RNA polymerase.

According to China National Center for Biotechnology Department, favipiravir (also known as favilavir or Avigan) is demonstrating encouraging profile with mild adverse reactions in COVID-19 patients in trials (findings of the trial are yet to be published).[135] It is reported to be the first approved drug for the treatment of COVID-19 in China. [136]

Favipiravir was reported to the media to have shown encouraging results in treating patients with COVID-19 in clinical trials involving 320 people in Shenzhen and Wuhan[137], and in-vitro studies of favipiravir showed that there was a high EC50 against SARS-CoV-2 of 61.88 µM/L in Vero E6 cells. [138]

An official at the Science and Technology Ministry in China reported that patients who were given Favipiravir in Shenzhen turned negative for the virus after a median of four days after becoming positive, compared with a median of 11 days for those who were not treated with Favipiravir. It was also stated that X-rays confirmed improvements in lung condition in about 91% of the patients who were treated with Favipiravir, compared to 62% or those not taking Favipiravir.[139] A journal article is being awaited.

Non-peer-reviewed results from a Chinese clinical trial stated that in ordinary COVID-19 patients untreated with antiviral previously, favipiravir has higher 7 day's clinical recovery rate and more effectively reduced incidence of fever, cough except some antiviral-associated

adverse effects. 120 patients were assigned to the favipiravir group (116 assessed) and 120 to the arbidol (umifenovir) group (120 assessed). Clinical recovery rate was 55.86% in the arbidol group and 71.43% in the favipiravir group. Patients with hypertension and/or diabetes, the time of fever reduction and cough relief in favipiravir group was significantly shorter than that in arbidol group, but there was no statistical difference was observed of auxiliary oxygen therapy or non-invasive mechanical ventilation rate. A key limitation cited was that among all the participants, there were 18 critical patients in the favipiravir group and 9 critical patients in the arbidol group. Because of the imbalance of the proportion of critical patients between the two groups, it had an important impact on the primary outcome (7 day's clinical recovery rate), secondary outcomes and combined medication.[140] This paper has not been peer reviewed.

Japan has announced plans to approve Favipiravir for treatment of COVID-19.[141]

Umifenovir

Sold under the brand name Arbidol, Umifenovir is an antiviral agent used in the treatment of influenza. It acts as an inhibitor that potentially disrupts the fusion of viral envelopes to host cells, thus inhibiting viral entry.[142] It is approved for use in only a few countries (eg China and Russia).[143] Umifenovir has been used to treat COVID-19 infections but its efficacy and safety remain unclear.[144] It is currently under clinical trials in China.

A study in China included 134 confirmed COVID-19 patients. Of these, 52 received lopinavir and ritonavir; 34 received arbidol (antiviral) and 48 were not given antivirals. Treatments were for seven days. All patients also received Interferon spray medication. After seven days there was no statistically significant difference in medical outcomes between the three groups.[145]

A nonrandomised study showed that patients who were treated with umifenovir for a median period of 9 days were associated with lower mortality rates and higher discharge rates. [146]

See clinical trial under favipiravir.[147]

Oseltamivir

Oseltamivir (Tamiflu) is used to treat influenza, this is one of the medications administered to patients in Singapore.[148] Research has yet to determine its effectiveness for COVID-19. It has been suggested that oseltamivirand other neuramindase inhibitors are ineffective against COVID-19.[149,150]

Baloxavir marboxil

Baloxavir marboxil (Xofluza) is a cap-dependent endonuclease inhibitor, and is tested in clinical trial in China.[151]

Repurposed Anti-Hepatitis Drugs

Ribavarin

Ribavarin functions as a broad-spectrum antiviral agent, and although it has been reported to have anti-MERS-CoV activity, the dose required results in toxicity.[152] Hence, treatment with lopinavir and ritonavir, with or without corticosteroids, are among the combinations employed. Efficacy of ribavirin against SARS-CoV has been assessed in observational studies, and a randomised controlled trial ranging from 7 to 1052 participants.[153]

Clinical trials are ongoing with ribavirin in combination with other drugs to treat COVID-19.

South Korean physician guidelines suggest considering the use of "ribavirin and interferon only if lopinavir/ritonavir or chloroquine or hydroxychloroquine does not work, or if the administration is impossible". This is due to the side effects. [154]

Sofosbuvir

In-vitro, Sofosbuvir has been found to bind to COVID-19 RNA dependent RNA polymerase.[155]

Beclabuvir

Beclabuvir was identified as candidates for COVID-19 therapy based on virtual high throughput screening of clinically approved drugs and the structure of SARS-CoV-2. Beclabuvir is an antiviral drug for the treatment of hepatitis C virus infection.[156]

Galidesivir

Biocryst Pharmaceuticals developed antiviral Galidesivir to treat Hepatitis C, which is in phase 1 clinical trial. It is evaluating it to determine if it could potentially target the coronavirus.[157] BCX-4430, a salt form of Galidesivir, is a potential drug for repurposing.[158]

Simeprevir

Simeprevir (Hepatitis C virus protease inhibitor) has been identified as a potential candidate to repurpose for COVID-19 infections.[159]

Repurposed Anti-parasitic Drugs

Nitazoxanide

Broad-spectrum antiparasitic and antiviral drug used to treat diarrhoea, was found to inhibit SARS-CoV-2 at a "low-micromolar concentration" in-vitro[160]. It may act by inhibiting the expression of viral proteins.[161]

Niclosamide

Niclosamide is a parasitic worm treatment. In a study it was found to have some impact in inhibiting SARS virus replication.[162]

Ivermectin

Ivermectin is an FDA-approved broad spectrum anti-parasitic medication. In-vitro, the drug demonstrated activity against different viruses including HIV, dengue, influenza and Zika. Study in vitro also finds the drug stops SARS-CoV-2 growing in cell culture within two days.[163]

Immunotherapies

SARS-CoV enters host cells through the binding of their spike (S) protein to angiotensin converting enzyme 2 (ACE2) and CD209L.[164] Human monoclonal antibodies to the S protein have been shown to significantly reduce the severity of lung pathology in non-human primates following MERS-CoV infection.[165] Such neutralising antibodies can be elicited by active or passive immunisation using vaccines or convalescent plasma respectively. While such neutralising antibodies can theoretically be harvested from individuals immunised with vaccines, it is not clear if therapeutic levels of antibodies can be obtained.

China has reported that it has cloned two human blocking mAbs using cells recovered from COVID-19 patients. These are reported to be able to bind to the S protein and block the virus.[166]

Eli Lilly and AbCellera starting research and development on identifying antibodies. Initial screening identified 500 or so fully human antibody sequences. With the project now advancing to an assessment of the antibodies' effectiveness against SARS-CoV-2.[167]

A trial where 10 severe patients treated with a single dose of convalescent plasma (200 ml) in addition to best supportive care and antivirals showed there was significant improvement in their symptoms and oxygen saturation within 3 days, with no severe effects noted. In 7 patients, viral levels also became negligible. The antivirals they received included arbidol, remdesivir, ribavirin or peramivir (not all were administered on each patient). [168]

REGN3048-3051

US Department of Health and Human Services and Regeneron Pharmaceuticals have put in place an expanded agreement around the use of Regeneron's VelocImmune® platform. The platform uses a unique genetically-engineered mouse with a humanised immune system that can be challenged with all or parts of a virus of interest. This aims to facilitate swift identification, preclinical validation and development of promising antibody candidates.[169] Regeneron Pharmaceuticals has developed monoclonal antibodies to treat MERS that are now being tested in early human studies.[170] With Ebola, it took Regeneron six months to develop candidate treatments and test them in animal models. A combination of REGN3048 and REGN3051 is slated for a human clinical trial sponsored by the US National Institute of Allergy and Infectious Diseases.[171]

IFX-1

Chinese authorities have approved clinical trials of IFX-1 anti-C5a monoclonal antibody produced by Beijing Staidson Biopharma and InflaRx as a COVID-19 treatment.[172]

Vir Biotechnology is working to rapidly determine whether previously identified anti-coronavirus monoclonal antibodies (mAbs) bind and neutralize SARS-CoV-2.[173]

Biopharmaceutical company Harbour BioMed has partnered Mount Sinai Health to produce monoclonal antibodies targeting SARS-CoV-2, leveraging on the H2L2 Harbour Mice platform. The monoclonal antibodies could be used to treat patients exposed to the virus, or confer prophylactic protection on those at a high risk of exposure, eg healthcare workers. These antibodies act by inhibiting the infection of cells.[174]

ImmunoPrecise Antibodies will use its B Cell Select™ and DeepDisplay™ discovery platforms to identify antibodies and therapeutic compounds against the coronavirus.[175] It will also tap on ImmunoPrecise's subsidiary Talem Therapeutics' access to the transgenic animal platform OmniAb® for direct generation of human antibodies. [176]

Brilacidin

Brilacidin by Innovation Pharmaceuticals is a candidate being evaluated as a potential treatment for coronavirus. Brilacidin has shown antibacterial, anti-inflammatory and immunomodulatory properties in several clinical trials.[177] Review articles suggest that immunomodulators, like Brilacidin could potentially act synergistically when combined with antivirals.[178,179]

Sirolimus

Sirolimus is an approved immunosuppressive drug for organ transplants. It is said reduce MERS-CoV infections by more than 60%[180], and improve the prognosis of patients with acute respiratory failure.[181] Based on network proximity analysis, a combination of sirolimus and dactinomycin has been proposed as a treatment for SARS-CoV-2 infections.[182]

Rintatolimod

Ampligen® produced by AIM ImmunoTech is an immune modulator indicated for severe chronic fatigue syndrome. There are early talks to consider its use as a prophylactic/early-onset therapeutic against COVID-19. [183]

Peptides

CEL-SCI has begun efforts to develop an immunotherapy for the potential treatment of Covid-19 coronavirus infection. The company will leverage its LEAPS peptide technology, which could enable immunotherapeutic peptides with antiviral, as well as anti-inflammatory effects. CEL-SCI notes that LEAPS peptides will use conserved regions of coronavirus proteins to induce protective cell-mediated T-cell responses and also decrease viral load. In addition to acting against the viral infection, these peptides should trigger an anti-inflammatory response. Previously, the LEAPS peptides were tested against another respiratory virus, called pandemic influenza (H1N1), in studies performed in alliance with the National Institutes for Allergies and Infectious Diseases (NIAID).[184]

Others

Ribonucleoside analogue

Ridgeback Biotherapeutics and Emory University's not-for-profit Drug Innovations at Emory (DRIVE) have partnered to develop a drug candidate for potential treatment of Covid-19. The partners aim to progress DRIVE's EIDD-2801 into human clinical trials. EIDD-2801 is an orally bioavailable version of a ribonucleoside analogue that blocks the replication of various RNA viruses such as SARS-CoV2.[185]

FDA has granted approval for human clinical trials.[186]

siRNAs

Alnylam Pharmaceuticals and Vir Biotechnology teamed up in March to develop RNAi therapeutics against the coronavirus behind the COVID-19 outbreak. The collaboration builds on Alnylam's synthesis of siRNAs that target highly conserved regions of coronavirus RNA.[187]

TMPRSS2 inhibitor (Camostat Mesylate)

SARS-CoV-2 infection depends on the host cell factors ACE2 and TMPRSS2. TMPRSS2 stands for "Transmembrane Protease Serine 2" and is a transmembrane protease of the serine protease family that is involved in many physiological and pathological processes. TMPRSS2 can be blocked by a clinically proven protease inhibitor, camostat mesylate. This drug is known to inhibit TMPRSS2, and therefore could theoretically prevent viral infection of the host cell via this transmembrane protease. This therefore could be a potential therapeutic agent for COVID-19 infection. Camostat mesylate has been approved in Japan for the treatment of pancreatic inflammation. When tested on SARS-CoV-2 isolated from a patient, camostat managed to prevent the entry of the virus into lung cells. [188,189]

Janus-associated kinase (JAK) inhibitors

Baricitinib, fedratinib, and ruxolitinib have been identified as potential candidates in a combination therapy approach - Baricitinib was thought to be the most promising.[190] Olumiant (baricitinib), approved for rheumatoid arthritis, was identified using machine learning algorithms on the basis of its inhibition of ACE2-mediated endocytosis. Another JAK inhibitor, Jakafi (ruxolitinib), is in trials (combined with mesenchymal stem cell infusion) for COVID-19.[191]

A lancet article suggests that Baricitinib could directly block the penetration of SARS-CoV-2 into host cells. [192]

Phase II study commencing to assess Janus Kinase (JAK) inhibitor tofacitinib in patients with SARS-CoV-2 interstitial pneumonia in Italy.[193]

CD24Fc

The US FDA has approved for OncoImmune to conduct a Phase III clinical trial of CD24Fc to treat patients hospitalised with COVID-19. CD24Fc modulates host inflammatory response to tissue injuries, believed to be involved in autoimmune disease, cancer, graft-versus-host disease (GvHD) and metabolic syndromes.[194]

High dose Vitamin C

High-dose vitamin C may result in immunosuppression of hyperactivation immune effector cells.[195]

This has been suggested as a possible therapeutic for COVID-19 infections.[196]

Zinc

In vitro study has found that increasing the intracellular Zn^{2+} concentration with zinc-ionophores like pyrithione (PT) can efficiently impair the replication of coronaviruses.[197] In vitro, chloroquine was found to be a zinc ionophore.[198]

Quercetin, another zinc ionophore anti-viral is also being explored as a potential treatment.[199] This was explored for potential use after the 2003 SARS outbreak.

It has been suggested that other possible drug candidates which could be repurposed and developed based on their potential to target Mpro. One study identified Prulifloxacin, Nelfinavir, Bictegravir, Tegobuvir and Bictegravir.[200] Another study identified Colistin, Valrubicin, Icatibant, Bepotastine, Epirubicin, Epoprostenol, Vapreotide, Aprepitant, Caspofungin, and Perphenazine.[201]

Another pre-publication paper has suggested that Azithromycin, Opipramol, Quinidine, and Omeprazole might be suitable for repurposing for the inhibition of SARS-CoV-2 based on in-vitro tests. [94]

Convalescent Plasma

The use of plasma obtained from recovering patients (convalescent plasma) has shown beneficial effects in outbreaks of SARS and influenza virus infections through reducing viral loads.[202,203]

China has started experimental treatment of convalescent plasma (CP) for COVID-19.[204]

It is suggested that CP may reduce respiratory viral load, reduce serum cytokine response and mortality. The total amount of transfusion for each adult was about 500 ml, and the transfusion was divided into two times. Each transfusion lasted for 20 min and was adjusted according to the patient's own conditions.[205] Clinical trials are required to determine efficacy and safety.

Treatment with convalescent plasma, while potentially promising, may have feasible challenges due of scalability linked to screening, recruitment and logistical challenges.[206]

Takeda, a Chinese company with a blood plasma unit, is working with authorities in Asia, Europe and the US to speed up the research and procure plasma from recovered patients who would have developed antibodies to the virus that could potentially mitigate severity of illness in COVID-19 patients and possibly prevent it.[207] TAK-888 is an anti-SARS-CoV-2

polyclonal hyperimmune globulin (H-IG) to treat high-risk individuals with COVID-19 which Takeda has developed.

Serological assay development research is progressing. Serological assays are of critical importance to determine seroprevalence in a given population, define previous exposure and identify highly reactive human donors for the generation of convalescent serum as therapeutic.[208]

UK Universities and the NHS Blood and Transplant are working towards starting clinical trials on using convalescent plasma to treat severe COVID-19 cases.[209]

Human Umbilical Cord Mesenchymal Stem Cells

Clinical trials are being undertaken.

Nanoviricide

NanoViricides, a clinical-stage company, is working on developing a treatment for COVID-19 using its nanoviricide® technology. The company's technology is used to develop ligands that can bind to the virus in the same way as a cognate receptor and attack various points of the virus.[210]

Synthetic Peptides & Small Molecules

Viral entry and fusion can be inhibited by synthetic peptides or small molecules which block the interaction between S protein and ACE2.[211,212] For example, the peptides can represent different regions of ACE2 or recombinant proteins that target specific regions of the S protein.[213] Such molecules act to inhibit viral attachment and entry into the host cells. Existing investigation is limited to experimental studies.

Molecules developed by Purdue University inhibit two coronavirus enzymes and prevent its replication. Researchers note that identified drugs may not be available to address the ongoing outbreak but they hope to make it accessible for future outbreaks.[214]

Q Biomed and Mannin Research are also co-developing a drug to treat vascular diseases in people with COVID-19. This is an "adjunct treatment for vascular leakage and endothelial dysfunction seen in COVID-19 and other infectious diseases", and is "designed to target the activation of the Angiopoietin-Tie2 signaling pathway".[215]

Drugs to Treat Acute Lung Injury and ARDS

One of the common complications in severe COVID-19 cases is acute respiratory distress syndrome (ARDS).[216] This can cause death and severe problems, and often leads to admission into critical care.

Corticosteroids

The use of corticosteroids for severe Acute Respiratory Distress Syndrome (ARDS) is controversial; therefore, glucocorticoids should be used cautiously. There are clinical trials being undertaken to determine the safety and efficacy of corticosteroid treatment for COVID-19 infections.

WHO states that clinicians should not routinely give systemic corticosteroids for treatment of viral pneumonia or ARDS outside of clinical trials unless they are indicated for another reason.[217] These other reasons may include asthma or COPD exacerbation, and sepsis (including septic shock).[218] Corticosteroids have been administered in patients mainly to

reduce the systemic inflammatory response of patients with severe pneumonia, reduce degree of dyspnoea, and also decrease the risk of ARDS.[219]

A retrospective study evaluated the effects of adjuvant corticosteroid treatment on the outcome of 244 critically ill patients with COVID-19, using a risk stratification model that adjusts for potential differences between the steroid group (n=151) and the non-steroid group (n=93). Adjuvant corticosteroid therapy was independent from 28-day mortality. However, increased corticosteroids dosage was significantly associated with elevated mortality risk after adjustment for administration duration; every ten-milligram increase in hydrocortisone-equivalent dosage was associated with additional 4% mortality risk.[220]

A retrospective study of 201 patients in China demonstrated the effectiveness of corticosteroid treatment in patients with ARDS. Those who received corticosteroids were associated with a lower risk of mortality (23/50 [46%] with steroids than 21/34 [62%] without; HR, 0.38 [95% CI, 0.20-0.72]). [221]

A retrospective preprint study done in France evaluated the effect of corticosteroids on orotracheal intubation in 70 patients with severe COVID-19 pneumonia (requiring at least 3 liters of oxygen). It was found that corticosteroids lowered the risk of intubation by 47.1%. However, this was not a randomised controlled trial. [222]

Singapore has avoided the use of corticosteroids, in view of increased mortality with their use in severe influenza.[223,224]

Monoclonal Antibody Drugs

Tocilizumab

Tocilizumab is a humanized monoclonal antibody which targets Interleukin 6 (IL-6), sold under the name Actemra. It is an immunosuppressive drug, used mainly for the treatment of rheumatoid arthritis. IL-6 is a cytokine that plays an important role in the immune response, and is therefore implicated in many immune mediated conditions. According to the FDA, Tocilizumab is also indicated for T-cell induced severe or life-threatening Cytokine Release Syndrome in adult patients and paediatric patients older than 2 years of age.[225] However, specific contraindications include active infections and localised infections. This would seem to indicate that Tocilizumab might not be suitable for use in COVID-19 patients.

Tocilizumab can specifically bind both membrane bound IL-6 receptor and soluble IL-6 receptor and inhibit signal transduction in the immune response. A clinical trial (ChiCTR2000029765) has seen inspiring clinical results in quickly decreasing body temperature and improved respiratory function.[226,227] Tocilizumab is presently under clinical trial in China and though to be of benefit to COVID-19 patients who show serious lung damage (in the setting of ALI) and show elevated levels of Interleukin 6, which could indicate inflammation or immunological diseases.[228,229] The latest study is a clinical trial evaluating its efficacy in an expected sample size of 188 participants.[230]

A pre-publication meta-analysis has shown that tocilizumab has appears to be efficacious and safe so far, but concludes that the above clinical trials need to be concluded before defining the role of the drug in COVID-19.[231]

In a case report from France, a patient with metastatic cancer was successfully treated with Tocilizumab after developing respiratory failure. He was simultaneously treated with lopinavir-ritonavir. [232] Similarly, there is also a case report of the 1st case of COVID-19 patient in China with multiple myeloma that has been successfully treated with tocilizumab. [233]

Namilumab

Namilumab is a human monoclonal antibody being developed to treat rheumatoid arthritis and ankylosing spondylitis. It is being studied under compassionate use for COVID-19.[234]

Siltuximab

Siltuximab, an interleukin (IL)-6 targeted monoclonal antibody is undergoing an observational case-controlled study for the treatment of patients with severe complications from COVID-19.[235]

Gimsilumab

Gimsilumab is a monoclonal antibody that targets GM-CSF, a pro-inflammatory cytokine found to be up-regulated in COVID-19 patients. Emerging clinical evidence in COVID-19 patients suggests that GM-CSF contributes to immunopathology in patients with or at risk of developing ARDS from COVID-19.[236]

TJM2

Clinical study commencing to explore the potential of TJM2 (I-Mab Biopharma) a proprietary mAb against GM-CSF, to treat cytokine storms associated with severe COVID-19 disease.[237]

Sarilumab (Kevzara)

Separately, Sanofi and Regeneron Pharmaceuticals currently have plans to initiate clinical trials of rheumatoid arthritis drug Kevzara for the treatment of Covid-19 symptoms. The US Food and Drug Administration (FDA) approved Kevzara in 2017 to treat rheumatoid arthritis. The drug inhibits IL-6, and is part of Sanofi and Regeneron's ongoing antibody partnership.[238]

Leronlimab

Leronlimab is a humanized IgG4 monoclonal antibody that is explored as a potential COVID-19 drug. The drug is being investigated in phase two clinical trials as a treatment for HIV and has been awarded fast-track approval status by the United States Food and Drug Administration.[239]

Foralumab

Foralumab is a fully human anti-CD3 mAb in clinical development. Tiziana Life Sciences is exploring development of this anti-interleukin-6 receptor (anti-IL6R) monoclonal antibody (mAb), TZLS-501, to treat COVID-19. Some COVID-19 patients experience an uncontrolled immune response called cytokine storm, which causes severe damage to lung tissue and progresses to respiratory failure. According to early clinical studies in China (data has not been confirmed), anti-IL6R mAbs may be used to treat COVID-19.[240]

Camrelizumab

Camrelizumab (humanized monoclonal antibody targeting PD-1) and thymosin (5-Da polypeptide hormone secreted by the thymus gland), are produced by Incyte, Shanghai Hengrui Pharmaceutical. These have been registered for testing in Chinese clinical trials.[241]

Fingolimod

Fingolimod is an immunomodulating drug, mostly used for treating multiple sclerosis. Clinical trial being undertaken.

Others

Anti-Vascular Endothelial Growth Factor (Bevacizumab)

VEGF is a protein secreted by alveolar cell-like lines in response to a number of pro-inflammatory stimuli, and has been implicated in acute respiratory distress syndrome (ARDS).[242] Bevacizumab, an anti-VEGF medication is in clinical trial as a promising drug for the treatment of acute lung injury as well as reduction of mortality in severe and critical COVID-19 patients through suppression of VEGF activity and therefore decreasing chances of ARDS occurring.[243]

BXT-25

BXT-25 by Bioxytran is explored for use as treatment for acute lung injury in late-stage patients infected with COVID-19. BX-25 is 5,000 times smaller than blood cells and transports oxygen through the body for a period of nine hours before being processed by the liver. The drug can help in supplying oxygen to the vital organs and enable the patient to recover and survive. [244]

Angiotension II inhibition

Angiotensin II is a substance produced normally by the body. Type 2 Pneumocytes (lung cells) need angiotensin II to mature. Proposed as a possible therapeutic mechanism for treatment of ARDS caused by SARS-CoV-2 infection. This is because alveolar type II pneumocyte apoptosis is stimulated by angiotensin II, and alveolar epithelial cell apoptosis might also be stimulated by angiotensin II.[245] Since pulmonary epithelial cell apoptosis is a common feature of ARDS and apoptosis of alveolar macrophages after viral infection amplifies the immune response and lung damage, inhibition of this pathway has been proposed as an effective treatment of ARDS secondary to SARS and COVID-19. [246,247]

Given this pathophysiology, angiotensin receptor blockers (or “sartans”) such as Olmesartan, could be explored to decrease rates of ARDS in COVID-19 infection. For example, a paper suggests angiotensin receptor 1 (AT1R) blockers, such as losartan, as therapeutics for reducing the aggressiveness and mortality from SARS-CoV-2 virus infections.[248] Furthermore, delivering excessive soluble form of ACE2 may slow viral entry into cells and viral spread and may protect the lung from injury.[249]

Patients receiving ACE inhibitor or ARB therapy was shown to have a lower rate of severe disease in SARS-CoV-2 infection and a trend toward a lower level of IL-6 in peripheral blood. Patients on ACE inhibitor or ARB therapy also had increased CD3 and CD8 T cell counts in peripheral blood and decreased peak viral load compared to patients on other antihypertensive drugs. [250]

In comparison, a report on the New England Journal of Medicine raised concerns over the role of renin-angiotensin-aldosterone system (RAAS) inhibitors in causing poor clinical outcomes, as some studies have suggested that these medications could increase ACE2 expression. However, there are inadequate studies being done to investigate the effects of RAAS inhibitors in COVID-19 patients. This report found that in patients with heart failure or past history of myocardial infarction, sudden discontinuation of RAAS inhibitors can lead to deterioration of their clinical condition and poor health outcomes. In light of this, until more reliable information is available, patients who are stable should continue their intake of RAAS inhibitors. Clinical trials are undergoing to determine efficiency and safety of recombinant human ACE2 and losartan in COVID-19. [251]

Recently published studies have also found that there was no significant association between the use of ARBs or ACE inhibitors and the risk of COVID-19, even after adjustment for possible confounders. [252] [253] A Spanish case-population study in the Lancet found that

RAAS inhibitors do not increase the risk of contracting COVID-19 and should be continued even in severe clinical cases. [254]

Recombinant Human Angiotensin-converting Enzyme 2 (rhACE2)

APN01 is a recombinant human Angiotensin Converting Enzyme 2 and was developed by Apeiron Biologics for the treatment of acute lung injury, acute respiratory distress syndrome and pulmonary arterial hypertension. A clinical trial is underway in China.[255,256]

Exogenous rhACE2 protein was shown to alleviate lung injury in experimental models. Soluble ACE2 can also neutralise the surface protein on SARS-CoV-2, which could prevent viral entry into lung pneumocytes.[257]

Pirfenidone

An idiopathic pulmonary fibrosis drug will be studied in patients with severe and critical COVID-19, under a planned randomised, open-label clinical trial in China.[258]

Thalidomide

Thalidomide is an immunomodulatory and anti-inflammatory drug and has been identified as a potential drug candidate.[259] It works by inhibiting TNF-alpha expression and therefore blunting the immune response. Thalidomide has been used to treat a number of cancers and skin conditions. Phase I and II clinical trial being undertaken to determine effectiveness in treating lung injury.

Bromhexine Hydrochloride

Bromhexine Hydrochloride is a mucolytic medication used to treat chest congestion and cough. It works by breaking down mucus so that it is easier to cough out. There is a clinical trial to determine its potential as a therapeutic in combination with other treatments.

Dehydroandrographolide succinate

Approved in China for the treatment of viral pneumonia and upper respiratory tract infections, is also used off-label in nebulisation therapy to avoid the adverse drug reactions associated with the injection. An animal in-vitro study suggested the nebulised drug has promise in treating lung injury.[260]

Nitric oxide gas therapy

Inhaled nitric oxide acts as a vasodilator, relaxing the lungs' muscles and blood vessels. Inhaled nitric oxide is being pursued as possible therapy. [261] It is currently undergoing clinical trials in China.[262]

Inhaled peptide

Bio-11006 is in clinical trial for ARDS.[263]

Activase

A paper was written proposing the use of tissue plasminogen activator (Activase), used to break up blood clots that cause strokes and heart attacks, might be able to help some patients who need a ventilator but can't get access.[264,265] This is because the pathophysiology of ARDS (including ARDS cases in COVID-19 patients) involves the deposition of fibrin in airspaces and lung parenchyma, along with fibrin-platelet microthrombi in pulmonary vasculature. All this can progress to respiratory dysfunction and right heart failure. As such, targeting the coagulation and fibrinolytic systems might theoretically negate the need for ventilator use in severely ill patients.

Famotidine

Famotidine, a H2 receptor inhibitor which acts on the parietal cells to suppress gastric acid secretion, is being trialed in New York as a potential therapy for Covid-19. Famotidine has been reported in China to be able to bind to an important enzyme in SARS-CoV2. As of 26 April 2020, 187 critically ill patients have been enrolled and they are looking to recruit 1174 patients. [266]

Alternative Medicines

Traditional Chinese Medicine is discussed as potential treatment.[267] There are national guidelines and provincial guidelines in China for the use of Chinese medicine for prevention, and during medical observation and treatment periods. These are detailed in a recent publication.[268]

A Chinese alternative medication known as “Shufeng Jiedu Capsule” may alleviate acute lung injury and warrants further study.[269,270] Several Traditional Chinese Medicines are in clinical trial for COVID-19 (eg T89, Huaier).

In vitro glycyrrhizin (a constituent of liquorice root), resveratrol (in grape seeds and red wine), silvestrol, and baicalin have been found to have some anti-viral effect on coronaviruses.[271,272,273,274]

Lianhua Qingwen, a Traditional Chinese Medicine, was reported to have shown to be effective in treating COVID-19. This drug could “weakly inhibit the virus and repair cell injuries and inflammation caused by the virus”. Recovery time, time taken for radiological findings to resolve and fever time were shortened with this treatment. [275]

In addition to Lianhua Qingwen, 2 additional TCM drugs, Jinhua Qinggan and Xuebijing, are being approved for use in Beijing. These have been used in over 70,000 patients across China and shown to reduce fever and inflammation. [276]

Broader Considerations

This report is *not* a clinical guideline – it does not make recommendations or cover detail on the specific treatment protocols.

The therapeutics outlined above are mainly for treatment of COVID-19 directly, or the management of its complications such as acute lung injury or ARDS. However, considerations need to be made at a broader level, most notably for prevention of viral illness and its complications, as well as supportive treatment to aid recovery of the patient post-infection.

The novelty of SARS-CoV-2 means that there is a lack of robust research specifically related to COVID-19 in general. Therefore, the points mentioned below remain as points of consideration.

Prevention

There is some indication that comorbidities as well as poor health practices may contribute to susceptibility of infection, or even severity of illness once infected. Risk factors might include pre-existing respiratory or cardiovascular conditions, smoking, alcohol consumption, poor diet, and decreased physical activity. Therefore, cessation or optimisation of such risk factors might play a part in treating COVID-19 patients. For a more in-depth look at current literature around comorbidities and poor health practices, please refer to the “Clinical Characteristics” report, in the “Sociodemographic Characteristics” section.

WHO has stated that tobacco increases the risk of suffering from COVID-19. People who have cardiovascular and respiratory conditions caused by tobacco use, or otherwise, are at higher risk of developing severe COVID-19 symptoms [277] US National Institute on Drug Abuse has also warned that those who those who smoke tobacco or marijuana or who vape may be especially at risk of COVID-19 infections.[278]

Research from China found the odds of a COVID-19 case becoming more severe, and at the most extreme, leading to death, are 14 times higher among people who had a history of smoking compared to those who did not smoke. Research has also found those with a history of smoking had a 14% higher risk of developing pneumonia.[279]

Treatment

Treatments for acute lung injury are outlined above, as this is one of the main serious complications of COVID-19.

Fever medications

Outlined in the clinical guidelines from China.[280]

Anti-inflammatory medications

A study published on Lancet suggested that the use of ibuprofen may increase angiotensin-converting enzyme 2 (ACE2), which is the receptor for the binding of coronaviruses to target cells. This may facilitate and worsen infections.[281] As a result, France advised the use of Panadol over other anti-inflammatory drugs in the event of fever. While NHS previously recommended both paracetamol and ibuprofen for symptomatic management, the guidance has been updated to take paracetamol unless otherwise indicated in the interim, although it was recognised that there is currently no strong evidence of the detrimental effects of ibuprofen.[282] WHO has provided similar advice while the evidence is further examined.[283]

It has been suggested that ACE-inhibitors, such as those used in the treatment of hypertension or diabetes and which raise ACE2 levels, may increase the risk of severe COVID-19 infection.[284] However, a small UK study found that treatment with ACE-inhibitors was associated with a reduced risk of rapidly deteriorating severe disease. There was a lower rate of death or transfer to a critical care unit within 7 days in patients on an ACE-inhibitor. A potential beneficial effect needs to be explored as more data becomes available.[285]

Nutrition support treatment

Cited in clinical guidelines in China and also studied under clinical trial.[286]

Oxygen therapy

Oxygen therapy is a common form of therapy given to patients who have trouble maintaining their oxygen saturations in their blood. This would most likely be a clinical decision made by clinicians directly treating the patients. The method of oxygen delivery would depend on severity, from supplementary oxygen through nasal prongs and masks, to invasive ventilation and extracorporeal membrane oxygenation (ECMO).[287,288]

Research from MERS suggests the use of ECMO as salvage treatment for patients with respiratory failure, as is the case for other respiratory infections.[289]

Fluid management

WHO states that patients should be treated cautiously with intravenous fluids. Overly aggressive fluid resuscitation may worsen oxygenation and cause further complications, especially in settings where there is limited availability of mechanical ventilation.[290,291]

Antibiotic therapy

A common complication of any viral pneumonia is a secondary overlying bacteria pneumonia. This is the case for some COVID-19 patients as well. Both the WHO and Chinese clinical guidelines cite the use of antibiotic therapy in certain situations.[292,293] However, the specific antibiotics and dosages used would be dependent primarily on the local guidelines and bacterial resistance patterns in the area.

Broad-spectrum antibiotics are commonly used in the management of MERS for empirical treatment of severe community-acquired pneumonia, as well as ventilator-associated bacterial pneumonia.[294]

Teicoplanin, a glycopeptide antibiotic that inhibits bacterial cell wall synthesis, was recently found to have actions against MERS-CoV and Ebola virus in cell culture.[295] The role of Teicoplanin in COVID-19 is still under investigation. [296]

A systematic review of 6 studies showed that there is no evidence to support the use of antibiotics in children with COVID-19 should they have no bacterial co-infection. [297]

Shock and sepsis

Treatment of septic shock is outlined in the WHO and Chinese guidelines.[298,299]

The management of **Stress ulcers and gastrointestinal bleeding** is considered in the clinical guidelines from China.[300]

Venous embolism is considered in the clinical guidelines from China.[301]

Statins, anti-arrhythmics, IL-1ra WHO stated that these are being studied in relation to care for seriously ill patients.[302]

Recovery

More research is required on considerations for care post-discharge.

Search Method

In January and February 2020, a systematic search was carried out in three major electronic databases (PubMed, Embase and Cochrane Library) to identify published studies examining the therapeutic drugs for Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and the 2019 novel coronavirus (2019-nCoV). Key words included “SARS”, “coronavirus”, “MERS”, “2019 Novel coronavirus”, “Wuhan virus”. Words “drug” and “therapy” were used in conjunction with the disease key words for the respective searches. This systematic review was a key component of a journal article (Pang J et al 2020) on the potential rapid diagnostics, vaccine and therapeutics for SARS-CoV-2.[303]

After the initial systematic review, weekly searches were undertaken on: WHO database on global research on coronavirus disease (COVID-19), PubMed, Google Scholar, pre-print server medRxiv, news outlets, specific journals and clinical trial sites. Key terms included “COVID”, “COVID-19”, “COVID19”, “coronavirus”, with “treatment” or “drug”. Articles were searched for treatment references.

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References

[1] WHO (2020) 2019 novel Coronavirus Global research and innovation forum: towards a research roadmap. Available at: https://www.who.int/blueprint/priority-diseases/key-action/Roadmap-version-FINAL-for-WEB.pdf?ua=1 (accessed 9.3.2020)
[2] Bill & Melinda Gates Foundation (2020) Bill & Melinda Gates Foundation, Wellcome, and Mastercard Launch Initiative to Speed Development and Access to Therapies for COVID-19. Available at: https://www.gatesfoundation.org/Media-Center/Press-Releases/2020/03/COVID-19-Therapeutics-Accelerator (accessed 8.2.2020)
[3] Wong SS, Yuen KY (2008) The management of coronavirus infections with particular reference to SARS. J Antimicrob Chemother. 62(3):437-41. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18565970 (accessed 25.2.2020)
[4] Talluri S (2020) Virtual High Throughput Screening Based Prediction of Potential Drugs for COVID-19. PrePrint. Available at: https://www.preprints.org/manuscript/202002.0418/v1 (accessed 5.3.2020)
[5] Liu X, Wang XJ (2020) Potential inhibitors for 2019-nCoV coronavirus M protease from clinically approved medicines. bioRxiv. Available at: https://www.biorxiv.org/content/10.1101/2020.01.29.924100v1 (accessed 24.2.2020)
[6] Zhang H et al (2020) Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med Available at: https://link.springer.com/article/10.1007/s00134-020-05985-9 (accessed 10.3.2020)
[7] Morse JS et al (2020) Learning from the Past: Possible Urgent Prevention and Treatment Options for Severe Acute Respiratory Infections Caused by 2019-nCoV. Chembiochem, 21 (5), 730-738. DOI: 10.1002/cbic.202000047. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32022370 (accessed 4.3.2020)
[8] STAT (2020) From ferrets to mice and marmosets, labs scramble to find right animals for coronavirus studies. March 5, 2020. Available at: https://www.statnews.com/2020/03/05/coronavirus-labs-scramble-to-find-right-animals-for-covid-19-studies/ (accessed 9.3.2020)
[9] Shi J et al (2020) Susceptibility of ferrets, cats, dogs, and different domestic animals to SARS-coronavirus-2. Available at: https://www.biorxiv.org/content/10.1101/2020.03.30.015347v1.full.pdf (accessed 2.4.2020)
[10] WHO (2020) Off-label use of medicines for COVID-19. March 31, 2020. Available at: https://apps.who.int/iris/bitstream/handle/10665/331640/WHO-2019-nCoV-Sci_Brief-Off-label_use-2020.1-eng.pdf (accessed 1.4.2020)
[11] University of Oxford (2020) The RECOVERY Trial. Available at: https://www.recoverytrial.net/ (accessed 13.4.2020)
[12] University of Oxford (2020) The RECOVERY Trial. Available at: https://www.recoverytrial.net/ (accessed 05.05.2020)
[13] Zhang Q et al (2020) Clinical trial analysis of 2019-nCoV therapy registered in China. J Med Virol. DOI: 10.1002/jmv.25733. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32108352 (accessed 4.3.2020)
[14] Zhu RF et al (2020) Systematic Review of the Registered Clinical Trials of Coronavirus Diseases 2019 (COVID-19). PrePrint. Available at: https://doi.org/10.1101/2020.03.01.20029611 (accessed 9.3.2020)
[15] Qiu R et al (2020) Outcome reporting in protocols of clinical trials of COVID-19 is inconsistent. PrePrint. Available at: https://doi.org/10.1101/2020.03.04.20031401 (accessed 9.3.2020)
[16] Belhadi D et al (2020) A brief review of antiviral drugs evaluated in registered clinical trials for COVID-19. Available at: https://doi.org/10.1101/2020.03.18.20038190 (Accessed 23.3.2020)
[17] STAT News (2020) WHO to launch multinational trial to jumpstart search for coronavirus drugs. March 18, 2020. Available at: https://www.statnews.com/2020/03/18/who-to-launch-multinational-trial-to-jumpstart-search-for-coronavirus-drugs/ (accessed 20.3.2020)
[18] WHO (2020) Clinical management of severe acute respiratory infection (SARI) COVID-19 disease is suspected. Interim guidance V1.2. 13 March 2020. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected (accessed 18.3.2020)
[19] Evidence Aid. Available at: https://www.evidenceaid.org/coronavirus-resources/ (accessed 19.3.2020)
[20] CDC (2020) Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html (accessed 1.4.2020)

[21] NICE (2020) Coronavirus (COVID-19). Available at: https://www.nice.org.uk/covid-19 (accessed 23.3.2020)
[22] NICE (2020) NICE updates rapid COVID-19 guideline on critical care, March 25, 2020. Available at: https://www.nice.org.uk/news/article/nice-updates-rapid-covid-19-guideline-on-critical-care (accessed 1.4.2020)
[23] National Health Service (2020) Acute use of non-steroidal anti-inflammatory aids (NSAIDs) for people with or without risk of COVID-19 (RPS2001). April 14, 2020. Available at: https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/04/C0211-NSAIDs-RPS_14-April.pdf (accessed 20.04.2020)
[24] National Institutes of Health (2020) Expert U.S. panel develops NIH treatment guidelines for COVID-19. April 21, 2020. Available at: https://www.nih.gov/news-events/news-releases/expert-us-panel-develops-nih-treatment-guidelines-covid-19 (accessed 05.05.2020)
[25] Cochrane Special Collections (2020) Coronavirus (COVID-19): evidence relevant to critical care Available at: https://www.cochranelibrary.com/collections/doi/SC000039/full (accessed 23.3.2020)
[26] Matthay MA et al (2020) Treatment for severe acute respiratory distress syndrome from COVID-19. Lancet. Available at: https://doi.org/10.1016/S2213-2600(20)30127-2 (accessed 23.3.2020)
[27] Ramanathan K et al (2020) Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. Lancet. Available at: https://doi.org/10.1016/S2213-2600(20)30121-1 (accessed 23.3.2020)
[28] Jason Phua J et al (2020) Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. Lancet. Available at: https://doi.org/10.1016/S2213-2600(20)30161-2 (accessed 13.4.2020)
[29] BMJ (2020) Coronavirus disease 2019 (COVID-19). Available at: https://bestpractice-bmj-com.libproxy1.nus.edu.sg/topics/en-gb/3000168/treatment-algorithm#patientGroup-0-0. (accessed 12.05.2020)
[30] Jin Y-H et al (2020) A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Military Medical Research. 7:4. Available at: https://mmrjournal.biomedcentral.com/articles/10.1186/s40779-020-0233-6 (accessed 24.2.2020)
[31] National Health Commission of the People's Republic of China (2020) Diagnosis and Treatment of Pneumonia Caused by 2019-nCoV (version 7) [Article in Chinese]. Available at http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml (accessed 18.3.2020)
[32] Kwak S-s et al (2020) Physicians work out treatment guidelines for coronavirus. Korean Biomedical Review. Available at: http://www.koreabiomed.com/news/articleView.html?idxno=7428 (accessed 11.3.2020)
[33] NCID (2020) Interim Treatment Guidelines for COVID-19 (Version 1.0, dated 2 April 2020 Singapore
[34] IDSA (2020) Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 Infection. Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ (accessed 13.4.2020)
[35] Wilson KC, Chotirmall SH, Bai C, Rello J (2020) COVID-19: Interim Guidance on Management Pending Empirical Evidence. Last updated April 3, 2020. Available at: https://www.thoracic.org/professionals/clinical-resources/disease-related-resources/covid-19-guidance.pdf (accessed 13.4.2020)
Task Force
[36] YNHHS (2020) Initial Treatment Algorithm for Hospitalized ADULTS with Non–Severe* COVID-19 Available at: https://medicine.yale.edu/intmed/COVID-19%20TREATMENT%20ADULT%20Algorithm%2004272020_382832_5_v4.pdf (accessed 13.4.2020)
[37] STAT News (2020) WHO to launch multinational trial to jumpstart search for coronavirus drugs. March 18, 2020. Available at: https://www.statnews.com/2020/03/18/who-to-launch-multinational-trial-to-jumpstart-search-for-coronavirus-drugs/ (accessed 20.3.2020)
[38] Ko WC et al (2020) Arguments in favor of remdesivir for treating SARS-CoV-2 infections International Journal of Antimicrobial Agents. DOI: https://doi.org/10.1016/j.ijantimicag.2020.105933. Available at: https://www.sciencedirect.com/science/article/pii/S0924857920300832?via%3Dihub (accessed 9.3.2020)
[39] Gordon CJ et al (2020) The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. Available at: https://www.jbc.org/content/early/2020/02/24/jbc.AC120.013056.full.pdf (accessed 10.3.2020)

[40] Liu W et al (2020) Learning from the Past: Possible Urgent Prevention and Treatment Options for Severe Acute Respiratory Infections Caused by 2019-nCoV. Available at: https://onlinelibrary.wiley.com/doi/epdf/10.1002/cbic.202000047 (accessed 24.2.2020)
[41] Wang M et al (2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res **30,** 269–271. February 4, 2020. Available at: https://doi.org/10.1038/s41422-020-0282-0 (accessed 17.3.2020)
[42] Baumann J (2020) Hundreds of Virus Patients Allowed to Try Gilead's Ebola Drug. March 11, 2020. Available at: https://news.bloomberglaw.com/pharma-and-life-sciences/hundreds-of-corona-patients-allowed-to-try-gileads-ebola-drug (accessed 18.3.2020)
[43] Sakoulas G (2020) Comment: Remdesivir: A Promising Antiviral Against Coronaviruses. March 3, 2020. NEJM Journal Watch. Available at: https://www.jwatch.org/na50889/2020/03/03/remdesivir-promising-antiviral-against-coronaviruses (accessed 10.3.2020)
[44] Grein J et al (2020) Compassionate Use of Remdesivir for Patients with Severe COVID-19. The New England Journal of Medicine. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2007016?query=featured_coronavirus (accessed 16.04.2020)
[45] Levenson E (2020) Remdesivir drug shows promise – but is far from a coronavirus cure. CNN. Available at: https://edition.cnn.com/2020/04/30/us/remdesivir-coronavirus-drug/index.html (accessed 02.05.2020)
[46] John H. Beigel, M.D. et al (2020) Remdesivir for the Treatment of Covid-19 — Preliminary Report. May 22, 2020. DOI: 10.1056/NEJMoa2007764. (accessed 26.05.2020)
[47] The Straits Times (2020) Gilead's remdesivir gets US emergency approval for Covid-19. May 3, 2020. Available at: https://www.straitstimes.com/world/united-states/gileads-remdesivir-gets-us-emergency-approval-for-covid-19 (accessed 05.05.2020)
[48] Wang Y et al (2020) Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31022-9/fulltext (accessed 30.04.2020)
[49] Momattin H et al (2019) A Systematic Review of therapeutic agents for the treatment of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Travel Med Infect Dis. 30:9-18. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31252170 (accessed 24.2.2020)
[50] Yao TT et al (2020) A Systematic Review of Lopinavir Therapy for SARS Coronavirus and MERS Coronavirus-A Possible Reference for Coronavirus Disease-19 Treatment Option. J Med Virol. 2020 Feb 27. DOI: 10.1002/jmv.25729. [Epub ahead of print] Available at: https://www.ncbi.nlm.nih.gov/pubmed/32104907 (accessed 4.3.2020)
[51] Liu C et al (2020) Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus disease. ACS Central Science. March 12, 2020. Available at: https://doi.org/10.1021/acscentsci.0c00272 (accessed 17.3.2020)
[52] ChinaBioToday (2020) Ascletis to start Zhejiang Province Trial of Generic HIV/AIDS Drug for COVID-19. February 17, 2020. Available at: http://www.chinabiotoday.com/articles/ascletis-zhejiang-covid19 (accessed 25.2.2020)
[53] Ibid Young BE et al (2020)
[54] Ibid Kwak S-s et al (2020)
[55] Ibid Jin Y-H et al (2020)
[56] Nature (2020) Therapeutic options for the 2019 novel coronavirus (2019-nCoV) February 10, 2020. Available at: https://www.nature.com/articles/d41573-020-00016-0?from=singlemessage (accessed 17.3.2020)
[57] Sixth Tone (2020) New Study Casts Doubt on Common COVID-19 Treatment. February 24, 2020. Available at: https://www.sixthtone.com/news/1005229/new-study-casts-doubt-on-common-covid-19-treatment (accessed 25.2.2020). Study in Chinese available at: http://rs.yiigle.com/yufabiao/1182592.htm (accessed 25.2.2020)
[58] Yan D et al (2020) Factors associated with prolonged viral shedding and impact of Lopinavir/Ritonavir
treatment in patients with SARS-CoV-2 infection. Available at: https://www.medrxiv.org/content/10.1101/2020.03.22.20040832v2.full.pdf (accessed 2.4.2020)
[59] Pharmaceutical Technology (2020) AbbVie to test HIV drug for Covid-19 treatment. March 11, 2020. Available at: https://www.pharmaceutical-technology.com/news/abbvie-hiv-drug-covid-19-treatment/ (accessed 12.3.2020)

[60] Cao B et al (2020) A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. NEJM. DOI: 10.1056/NEJMoa2001282. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2001282 (accessed 20.3.2020)
[61] Hung, Ivan Fan-Ngai et al. (2020). Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. DOI: https://doi.org/10.1016/S0140-6736(20)31042-4. (accessed 12.05.2020)
[62] Encyclopaedia Britannica (2020) Interferon. Available at: https://www.britannica.com/science/interferon (accessed 25.2.2020)
[63] Shen K et al (2020) Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World Journal of Pediatrics, 1-9. DOI:10.1007/s12519-020-00343-7. Available at: https://www.semanticscholar.org/paper/Diagnosis%2C-treatment%2C-and-prevention-of-2019-novel-Shen-Yang/6d1ee138c9497ef8e99bd3994f04ac5505212a92 (accessed 24.2.2020)
[64] Ibid Jin Y-H et al (2020)
[65] GEN (2020) How to Conquer Coronavirus: Top 35 Treatments in Development. March 2, 2020. Available at: https://www.genengnews.com/a-lists/how-to-conquer-coronavirus-top-35-treatments-in-development/ (accessed 13.3.2020)
[66] Zhou Q. et al (2020) Interferon-a2b treatment for COVID-19. medRxiv 2020.04.06.20042580; doi: https://doi.org/10.1101/2020.04.06.20042580 (accessed 21.04.2020)
[67] Pharmafield (2020) Synairgen to start trial of SNG001 in COVID-19. Available at: https://pharmafield.co.uk/pharma_news/synairgen-to-start-trial-of-sng001-in-covid-19/. (accessed 28.04.2020)
[68] Gao J et al (2020) Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. BioScience Trends DOI: 10.5582/bst.2020.01047. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32074550 (accessed 24.2.2020)
[69] Huang M et al(2020) Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. Expert Consensus on Chloroquine Phosphate for the Treatment of Novel Coronavirus Pneumonia. Zhonghua Jie He He Hu Xi Za Zhi. 2020;43(0):E019. DOI: 10.3760/cma.j.issn.1001-0939.2020.0019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32075365 (accessed 24.2.2020)
[70] Zhi et al (2020) Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. 2020 Feb 20;43(0):E019. DOI: 10.3760/cma.j.issn.1001-0939.2020.0019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32075365/ (accessed 11.3.2020)
[71] Keyaerts E et al (2004) In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun. 323(1):264-8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15351731 (accessed 24.2.2020)
[72] Savarino A et al (2003) Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis. 3:722- 727. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14592603 (accessed 24.2.2020)
[73] Yan Y et al (2013) Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model. Cell Res. 23:300-302. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3567830/ (accessed 24.2.2020)
[74] Colson P (2020) Chloroquine and hydroxychloroquine as available weapons to fight COVID-19 International Journal of Antimicrobial Agents. Available at: https://doi.org/10.1016/j.ijantimicag.2020.105932 (accessed 9.3.2020)
[75] R. Mccall (2020) Some Swedish Hospitals have stopped using chloroquine to treat COVID-19 after reports of severe side effects. Available at: https://www.newsweek.com/swedish-hospitals-chloroquine-covid-19-side-effects-1496368 (accessed 7.4.2020)
[76] Borba et al (2020) Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). Available at: https://www.medrxiv.org/content/10.1101/2020.04.07.20056424v1.full.pdf (accessed 13.4.2020)
[77] Giudicessi JR et al (2020) Urgent Guidance for Navigating and Circumventing the QTc-Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for Coronavirus Disease 19 (COVID-19) Available at: https://doi.org/10.1016/j.mayocp.2020.03.024 (accessed 13.4.2020)

[78] Kapoor A et al (2020) Cardiovascular risks of hydroxychloroquine in treatment and prophylaxis of COVID-19 patients: A scientific statement from the Indian Heart Rhythm Society. Available at: https://doi.org/10.1016/j.ipej.2020.04.003 (accessed 13.3.2020)
[79] Ibid Kwak S-s et al (2020)
[80] Yao X et al (2020) In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020 Mar 9. pii: ciaa237. DOI: 10.1093/cid/ciaa237. [Epub ahead of print] Available at: https://www.ncbi.nlm.nih.gov/pubmed/32150618 (accessed 13.3.2020)
[81] Clinical Trials (2020) NCT04307693 Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients with Mild Coronavirus Disease (COVID-19). Available at: https://clinicaltrials.gov/ct2/show/NCT04307693 (accessed 18.3.2020)
[82] Clinical Trials (2020) NCT04261517 Efficacy and Safety of Hydroxychloroquine for Treatment of Pneumonia Caused by 2019-nCov (HC-nCov). Available at: https://clinicaltrials.gov/ct2/show/NCT04261517 (accessed 18.3.2020)
[83] RTV (2020) Article in Dutch. Available at: https://www.rtvnoord.nl/nieuws/220259/RUG-onderzoeker-ontwikkelt-coronamedicijn-door (accessed 20.3.2020)
[84] Chen Z et al (2020) Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. Available at: https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v2.full.pdf (accessed 2.4.2020)
[85] Mahevas M. et al (2020) No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. medRxiv 2020. doi: https://doi.org/10.1101/2020.04.10.20060699 (accessed 21.04.2020)
[86] Wei T. et al (2020) Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. medRxiv. Doi: https://doi.org/10.1101/2020.04.10.20060558 (accessed 21.04.2020)
[87] Geleris et al (2020) Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. May 7, 2020. DOI: 10.1056/NEJMoa2012410 (accessed 12.05.2020)
[88] Rubin et al (2020) The Urgency of Care during the Covid-19 Pandemic — Learning as We Go. May 7, 2020. DOI: 10.1056/NEJMe2015903 (accessed 12.05.2020)
[89] Tang Wei, Cao Zhujun, Han Mingfeng, Wang Zhengyan, Chen Junwen, Sun Wenjin et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial BMJ 2020; 369 :m1849. DOI: https://doi.org/10.1136/bmj.m1849. (accessed 26.05.2020)
[90] AA (2020) Russia claims it produces drug to treat COVID-19. March 28, 2020. Available at: https://www.aa.com.tr/en/latest-on-coronavirus-outbreak/russia-claims-it-produces-drug-to-treat-covid-19-/1783292 (accessed 1.4.2020)
[91] Channel News Asia (2020) COVID-19: WHO suspends trial of hydroxychloroquine due to safety concerns. May 26, 2020. Available at: https://www.channelnewsasia.com/news/world/covid-19-who-suspends-trial-of-hydroxychloroquine-due-to-safety-12768360?utm_source=dlvr.it&utm_medium=twitter (accessed 26.05.2020)
[92] Molina JM et al (2020) No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection, Medecine et Maladies Infectieuses. Available at: https://doi.org/10.1016/j.medmal.2020.03.006 (accessed 5.4.2020)
[93] CDC (2020) Information for Clinicians on Therapeutic Options for COVID-19 Patients. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html (accessed 23.3.2020)
[94] Touret et al (2020) In vitro screening of a FDA approved chemical library reveals potential inhibitors of SARS-CoV-2 replication. Available at: https://doi.org/10.1101/2020.04.03.023846 (accessed 7.4.2020)
[95] Pharmaceutical Technology (2020) Pfizer identifies lead coronavirus drug candidate. April 10, 2020. Available at: https://www.pharmaceutical-technology.com/news/pfizer-identifies-lead-coronavirus-drug-candidate/ (accessed 13.4.2020)
[96] Mehra, Mandeep R et al. (2020) Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. May 22, 2020. DOI: https://doi.org/10.1016/S0140-6736(20)31180-6. (accessed 26.05.2020)
[97] J Watson et al (2020) An open letter to Mehra et al and The Lancet. Available at: https://zenodo.org/record/3864691#.XtOGvi-w2Cd (accessed 31.05.2020)
[98] M O'Riordan (2020) Lancet COVID-19 Hydroxychloroquine Study Faces 'Data Integrity' Questions. Available at: https://www.tctmd.com/news/lancet-covid-19-hydroxychloroquine-study-faces-data-integrity-questions (accessed 31.05.2020)

[99] CBS (2020) Coronavirus cannot be cured by drinking bleach or snorting cocaine, despite social media rumors. March 9, 2020. https://www.cbsnews.com/news/coronavirus-drinking-bleach-cocaine-false-rumors-social-media/ (accessed 1.4.2020)
[100] CBS (2020) Coronavirus cannot be cured by drinking bleach or snorting cocaine, despite social media rumors. March 9, 2020. https://www.cbsnews.com/news/coronavirus-drinking-bleach-cocaine-false-rumors-social-media/ (accessed 1.4.2020)
[101] WHO (2020) Myth-busters. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/myth-busters (accessed 1.4.2020)
[102] Independent (1010) Coronavirus: Hundreds dead in Iran from drinking methanol amid fake reports it cures disease. Available at: https://www.independent.co.uk/news/world/middle-east/iran-coronavirus-methanol-drink-cure-deaths-fake-a9429956.html (accessed 1.4.2020)
[103] NYT (2020) Covid-19 Has Closed Stores, but Snake Oil Is Still for Sale. March 31, 2020. https://www.nytimes.com/2020/03/31/opinion/fake-treatment-cure-coronavirus.html (accessed 1.4.2020)
[104] CBS (2020) Coronavirus cannot be cured by drinking bleach or snorting cocaine, despite social media rumors. March 9, 2020. https://www.cbsnews.com/news/coronavirus-drinking-bleach-cocaine-false-rumors-social-media/ (accessed 1.4.2020)
[105] Channel News Asia (2020) Trump's COVID-19 disinfectant ideas horrify health experts. Available at: https://www.channelnewsasia.com/news/world/doctors-say-trump-disinfectant-comments-dangerous-12674630 (accessed 25.04.2020)
[106] Telegraph (2020) Coronavirus myths, scams and conspiracy theories that have gone viral. March 29, 2020. Available at: https://www.telegraph.co.uk/global-health/climate-and-people/coronavirus-myths-scams-conspiracy-theories-true-false-lab-leak/ (accessed 1.4.2020)
[107] Telegraph (2020) Coronavirus myths, scams and conspiracy theories that have gone viral. March 29, 2020. Available at: https://www.telegraph.co.uk/global-health/climate-and-people/coronavirus-myths-scams-conspiracy-theories-true-false-lab-leak/ (accessed 1.4.2020)
[108] Telegraph (2020) Coronavirus myths, scams and conspiracy theories that have gone viral. March 29, 2020. Available at: https://www.telegraph.co.uk/global-health/climate-and-people/coronavirus-myths-scams-conspiracy-theories-true-false-lab-leak/ (accessed 1.4.2020)
[109] Malaysia Kini (2020) Poison Centre: 'Health tag' for preventing Covid-19 ineffective. March 30, 2020. Available at: https://www.malaysiakini.com/news/517728 (accessed 1.4.2020)
[110] FDA (2020) Coronavirus Update: FDA and FTC Warn Seven Companies Selling Fraudulent Products that Claim to Treat or Prevent COVID-19. March 9, 2020. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-update-fda-and-ftc-warn-seven-companies-selling-fraudulent-products-claim-treat-or?utm_campaign=030920_Statement_FDA%20and%20FTC%20Warn%20Companies%20for%20False%20Claims%20of%20Treating%20COVID-19&utm_medium=email&utm_source=Eloqua (accessed 1.4.2020)
[111] CIDRAP (2020) Experts say COVID-19 will likely lead to US drug shortages. Available at: https://www.cidrap.umn.edu/news-perspective/2020/03/experts-say-covid-19-will-likely-lead-us-drug-shortages (accessed 13.4.2020)
[112] EMA (2020) EU authorities agree new measures to support availability of medicines used in the COVID-19 pandemic Share. Press release April 6, 2020. Available at: https://www.ema.europa.eu/en/news/eu-authorities-agree-new-measures-support-availability-medicines-used-covid-19-pandemic (accessed 13.4.2020)
[113] FT (2020) Medical groups warn of serious shortages of hydroxychloroquine. April 7, 2020. Available at: https://www.ft.com/content/e0acace3-051d-4801-af6c-3a5a5e05aac6 (accessed 13.4.2020)
[114] Luis et al (2020) Evolving ART crisis for people living with HIV in Indonesia. Available at: https://doi.org/10.1016/S2352-3018(20)30138-7 (accessed 05.05.2020)
[115] CDC (2020) Information for Clinicians on Therapeutic Options for COVID-19 Patients. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html (accessed 23.3.2020)
[116] Mitjà O, Clotet B (2020) Use of antiviral drugs to reduce COVID-19 transmission. Lancet. Available at: https://doi.org/10.1016/S2214-109X(20)30114-5 (accessed 23.3.2020)
[117] Agrawal et al (2020) Emerging prophylaxis strategies against COVID-19. Available at: https://www.monaldi-archives.org/index.php/macd/article/view/1289/1005 (accessed 8.4.2020)
[118] The Hindu (2020) BMC to try out hydroxychloroquine as prophylaxis in Dharavi, Worli Koliwada. April 14, 2020. Available at: https://www.thehindu.com/news/cities/mumbai/bmc-to-try-out-hydroxychloroquine-as-prophylaxis-in-dharavi-worli-koliwada/article31335133.ece (accessed 05.05.2020)

[119] Park SY et al (2019) Post-exposure prophylaxis for Middle East respiratory syndrome in healthcare workers. Shi H J Hosp Infect. Jan; 101(1):42-46. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30240813 (accessed 29.1.2020)
[120] Zhang J et al (2020) Potential of arbidol for post-exposure prophylaxis of COVID-19 transmission-preliminary report of a retrospective case-control study. Available at: http://www.chinaxiv.org/user/download.htm?id=30258 (accessed 9.4.2020)
[121] Shi Q. (2020) Potential Effectiveness and Safety of Antiviral Agents in Children with Coronavirus Disease 2019: A Rapid Review and Meta-Analysis. MedRxiv 2020. doi: https://doi.org/10.1101/2020.04.13.20064436 (accessed 21.04.2020)
[122] Meng et al (2020). An experimental trial of recombinant human interferon alpha nasal drops to prevent coronavirus disease 2019 in medical staff in an epidemic area. medRxiv 2020.04.11.20061473; Available at: https://doi.org/10.1101/2020.04.11.20061473 (accessed 18.04.2020)
[123] Pinto et al (2020). Structural and functional analysis of a potent sarbecovirus neutralizing antibody. bioRxiv 2020.04.07.023903; doi: https://doi.org/10.1101/2020.04.07.023903 (accessed 18.04.2020)
[124] Clinical Trials Arena (2020) Coronavirus treatment: Vaccines/drugs in the pipeline for Covid-19. March 2, 2020. February 21, 2020. Available at: https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/ (accessed 3.3.2020)
[125] Ibid GEN (2020)
[126] Dong, L., Hu, S., & Gao, J. (2020). Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discoveries & Therapeutics, 14(1), 58–60. https://doi.org/10.5582/ddt.2020.01012 (accessed 21.04.2020)
[127] Profile Meyer SD et al (2020) Lack of Antiviral Activity of Darunavir against SARS-CoV-2. PrePrint. Available at: https://doi.org/10.1101/2020.04.03.20052548 (accessed 9.4.2020)
[128] J&J (2020) Lack of evidence to support use of darunavir-based treatments for SARS-CoV-2. Available at: https://www.jnj.com/lack-of-evidence-to-support-darunavir-based-hiv-treatments-for-coronavirus (accessed 9.4.2020)
[129] Jockusch et al (2020) Triphosphates of the Two Components in DESCOVY and TRUVUDA are Inhibitors of SARS-CoV-2 Polymerase. Available at: https://doi.org/10.1101/2020.04.03.022939 (accessed 7.4.2020)
[130] Chinese Clinical Trial Registry (2020) ChiCTR2000029468 A real-world study for lopinavir/ritonavir (LPV/r) and emtritabine (FTC) / Tenofovir alafenamide Fumarate tablets (TAF) regimen in the treatment of novel coronavirus pneumonia (COVID-19). Available at: www.chictr.org.cn/showprojen.aspx?proj=48919 (accessed 18.3.2020)
[131] Ibid Talluri S (2020)
[132] Chinese Clinical Trial Registry (2020) ChiCTR2000030424 A single-center, single-arm clinical trial for azvudine in the treatment of novel coronavirus pneumonia (COVID-19) Available at: http://www.chictr.org.cn/showproj.aspx?proj=50174 (accessed 18.3.2020)
[133] Fintelman-Rodrigues et al (2020) Atazanavir inhibits SARS-CoV-2 replication and pro-inflammatory cytokine production. Available at: https://doi.org/10.1101/2020.04.04.020925 (accessed 7.4.2020)
[134] BioWorld (2020) Fujifilm stock rises as Japan considers Avigan for COVID-19 treatment. Available at: https://www.bioworld.com/articles/433290-fujifilm-stock-rises-as-japan-considers-avigan-for-covid-19-treatment (accessed 26.2.2020)
[135] Clinical Trials Arena (2020) Favilavir approved as experimental coronavirus drug. February 21, 2020. Available at: https://www.clinicaltrialsarena.com/news/china-favilavir-testing-approval/ (accessed 3.3.2020)
[136] Pharmaceutical Technology (2020) China approves first anti-viral drug against coronavirus Covid-19. February 18, 2020. Available at: https://www.pharmaceutical-technology.com/news/china-approves-favilavir-covid-19/ (accessed 18.3.2020)
[137] Independent (2020) Coronavirus: Japanese anti-viral drug effective in treating patients, Chinese official says. Available at: https://www.independent.co.uk/news/world/asia/coronavirus-treatment-anti-viral-drug-favipiravir-avigan-wuhan-china-a9408066.html (accessed 19.3.2020)
[138] Sanders, J. M., Monogue, M. L., Jodlowski, T. Z., & Cutrell, J. B. (2020). Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA. https://doi.org/10.1001/jama.2020.6019 (accessed 21.04.2020)
[139] Guardian (2020) Japanese flu drug 'clearly effective' in treating coronavirus, says China. March 18, 2020. Available at: https://www.theguardian.com/world/2020/mar/18/japanese-flu-drug-clearly-effective-in-treating-coronavirus-says-china (accessed 20.3.2020)
[140] Chen C et al (2020) Favipiravir versus Arbidol for COVID-19: A Randomized Clinical

Trial. PrePrint. Available at: https://www.medrxiv.org/content/10.1101/2020.03.17.20037432v1.full.pdf (accessed 23.3.2020)
[141] CAN (2020) Japan's Abe vows unprecedented stimulus as Tokyo COVID-19 cases rise. March 28, 2020. Available at: https://www.channelnewsasia.com/news/asia/japan-abe-vows-unprecedented-stimulus-covid-19-coronavirus-12585972 (accessed 1.4.2020)
[142] Ibid Liu C et al (2020)
[143] Huang L et al (2017) Arbidol for preventing and treating influenza in adults and children. Cochrane Library 2017(2): CD011489. Available at: https://www.cochrane.org/CD011489/ARI_arbidol-preventing-and-treating-influenza-adults-and-children (accessed 18.3.2020)
[144] Sinelschikova Y (2020) China to treat coronavirus with a SOVIET drug that even Russia has doubts about. Russia Beyond. Available at: https://www.rbth.com/lifestyle/331736-china-coronavirus-russian-arbidol (accessed 24.2.2020)
[145] Ibid Sixth Tone (2020)
[146] Wang Z et al (2020) Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Available at: https://doi.org/10.1093/cid/ciaa272 (accessed 23.04.2020)
[147] Chen C et al (2020) Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. PrePrint. Available at: https://www.medrxiv.org/content/10.1101/2020.03.17.20037432v1.full.pdf (accessed 23.3.2020)
[148] Ibid Young BE et al (2020)
[149] Wang D et al (2020) Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA.2020;323(11):1061-1069. Available at: DOI:10.1001/jama.2020.1585 (accessed 18.3.2020)
[150] Li H et al (2020) Potential Antiviral Therapuetics for 2019 Novel Coronavirus [Article in Chinese]. Chin J Tuberc Respir Dis. 2020;43(0):E002. Available at: https://pubmed.ncbi.nlm.nih.gov/32023685/ (accessed 18.3.2020)
[151] Harrison C (2020) Coronavirus puts drug repurposing on the fast track. Nature Biotechnology. February 27, 2020. Available at: https://www.nature.com/articles/d41587-020-00003-1 (accessed 4.3.2020)
[152] Hart BJ et al (2020) Interferon-β and mycophenolic acid are potent inhibitors of Middle East respiratory syndrome coronavirus in cell-based assays. J Gen Virol. 2014;95:571–577. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3929173/ (accessed 18.3.2020)
[153] Momattin H et al (2013) Therapeutic options for Middle East respiratory syndrome coronavirus (MERS-CoV) possible lessons from a systematic review of SARS-CoV therapy. Int J Infect Dis. 17(10):e792-8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23993766 (accessed 24.2.2020)
[154] Ibid Kwak S-s et al (2020)
[155] Elfiky A A (2020) Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sciences. Available at: https://www.sciencedirect.com/science/article/pii/S0024320520302253?via%3Dihub (accessed 18.3.2020)
[156] Ibid Talluri S (2020)
[157] The Motley Fool (2020) 5 Biotech Stocks to Watch With the Coronavirus Scare. But it's important to separate the current panic from the real potential for these biotechs. By Speights K. January 26, 2020. Available at: https://www.fool.com/investing/2020/01/26/5-biotech-stocks-to-watch-with-the-coronavirus-sca.aspx (accessed 29.1.2020)
[158] Ibid Liu C et al (2020)
[159] Hosseini F, Amanlou M (2020) Simeprevir, Potential Candidate to Repurpose for Coronavirus Infection: Virtual Screening and Molecular Docking Study. Online: 28 February 2020. PrePrint. Available at: https://www.preprints.org/manuscript/202002.0438/v1 (accessed 3.5.2020)
[160] Ibid Wang M et al (2020)
[161] Ibid Liu C et al (2020)
[162] Wu CJ et al (2004) Inhibition of severe acute respiratory syndrome coronavirus replication by niclosamide. Antimicrob Agents Chemother. 48(7):2693-6. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC434198/ (Accessed 24.2.2020)
[163] Caly L et al (2020) The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. Available at: https://doi.org/10.1016/j.antiviral.2020.104787 (accessed 13.4.2020)
[164] Wong SS, Yuen KY (2008) The management of coronavirus infections with particular reference to SARS. J Antimicrob Chemother. 62(3):437-41. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18565970 (accessed 25.2.2020)
[165] Johnson RF et al (2016) 3B11-N, a monoclonal antibody against MERS-CoV, reduces lung pathology in rhesus monkeys following intratracheal inoculation of MERS-CoV Jordan-n3/2012.

Virology. 490:49-58. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26828465 (accessed 24.2.2020)
[166] Chen et al (2020) Human monoclonal antibodies block the binding of SARS-CoV-2 spike protein to angiotensin converting enzyme 2 receptor medRxiv 2020.04.06.20055475; Available at: https://doi.org/10.1101/2020.04.06.20055475 (accessed 13.4.2020)
[167] Fierce Biotech (2020) Biopharma's leading treatment hopes against COVID-19. March 20, 2020. Available at: https://www.fiercebiotech.com/biotech/biopharma-s-leading-treatment-hopes-against-covid-19 (accessed 24.3.2020)
[168] Duan K. et al (2020) Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A. 2020; 117(17):9490-9496. doi: 10.1073/pnas.2004168117 (accessed 05.05.2020)
[169] Regeneron Pharmaceuticals (2020) Regeneron announces expanded collaboration with HHS to develop antibody treatments for new coronavirus. February 4, 2020. Available at: https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-announces-expanded-collaboration-hhs-develop-antibody (accessed 3.3.2020)
[170] Science Mag (2020) Can an anti-HIV combination or other existing drugs outwit the new coronavirus? https://www.sciencemag.org/news/2020/01/can-anti-hiv-combination-or-other-existing-drugs-outwit-new-coronavirus (accessed 29.1.2020)
[171] Clinical Trials Arena (2020) Coronavirus treatment: Vaccines/drugs in the pipeline for Covid-19. March 11, 2020. February 21, 2020. Available at: https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/ (accessed 18.3.2020)
[172] Ibid GEN (2020)
[173] VIR (2020) Press Release Details: Vir Biotechnology applying multiple platforms to address public health risk from Wuhan coronavirus. January 22, 2020. Available at: https://investors.vir.bio/news-releases/news-release-details/vir-biotechnology-applying-multiple-platforms-address-public (accessed 29.1.2020)
[174] Pharmaceutical Technology (2020) Harbour BioMed, Mount Sinai to develop Covid-19 therapies. March 9, 2020. Available at: https://www.pharmaceutical-technology.com/news/harbour-biomed-sinai-covid-19-drugs/ (accessed 12.3.2020)
[175] Clinical Trials Arena (2020) Coronavirus treatment: Vaccines/drugs in the pipeline for Covid-19. March 2, 2020. February 21, 2020. Available at: https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/ (accessed 3.3.2020)
[176] Ibid GEN (2020)
[177] Clinical Trials Arena (2020) Coronavirus treatment: Vaccines/drugs in the pipeline for Covid-19. March 2, 2020. February 21, 2020. Available at: https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/ (accessed 3.3.2020)
[178] Innovations Pharmaceuticals (2020) Shareholder Alert: Scientific Rationale for Brilacidin as a Potential Novel Coronavirus (COVID-19) Treatment February 28, 2020. Available at: http://www.ipharminc.com/new-blog/2020/2/28/shareholder-alert-scientific-rationale-for-brilacidin-as-a-potential-novel-coronavirus-covid-19-treatment (accessed 4.3.2020)
[179] Zumla A et al (2016) Coronaviruses – drug discovery and therapeutic options. Nature Reviews Drug Discovery volume 15, pages327–347(2016)Available at: https://www.nature.com/articles/nrd.2015.37 (accessed 4.3.2020)
[180] Dyall J et al (2017) Middle East respiratory syndrome and severe acute respiratory syndrome: current therapeutic options and potential targets for novel therapies. Drugs **77**, 1935–1966 (2017). Available at: https://link.springer.com/article/10.1007%2Fs40265-017-0830-1 (accessed 18.3.2020)
[181] Wang CH et al (2014) Adjuvant treatment with a mammalian target of rapamycin inhibitor, sirolimus, and steroids improves outcomes in patients with severe H1N1 pneumonia and acute respiratory failure. Crit. Care Med. 42, 313–321 Available at: https://www.ncbi.nlm.nih.gov/pubmed/24105455?dopt=Abstract (accessed 18.3.2020)
[182] Zhou Y et al (2020) Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. Cell Discov 6, 14. Available at: https://doi.org/10.1038/s41421-020-0153-3 (accessed 18.3.2020)
[183] Ibid GEN (2020)
[184] Pharmaceutical Technology (2020) EL-SCI to develop Covid-19 immunotherapy. March 11, 2020. Available at: https://www.pharmaceutical-technology.com/news/cel-sci-covid-19-immunotherapy/ (accessed 12.3.2020)
[185] Pharmaceutical Technology (2020) Ridgeback Biotherapeutics and DRIVE to develop Covid-19 drug. March 20, 2020. https://www.pharmaceutical-technology.com/news/ridgeback-biotherapeutics-covid-19/ (accessed 23.3.2020)

[186] Pharmaceutical Technology (2020) FDA authorises Emory University to trial antiviral for Covid-19. April 8, 2020. Available at: https://www.pharmaceutical-technology.com/news/emory-university-covid-trial-fda-approval/ (accessed 13.4.2020)
[187] Fierce Biotech (2020) Biopharma's leading treatment hopes against COVID-19. March 20, 2020. Available at: https://www.fiercebiotech.com/biotech/biopharma-s-leading-treatment-hopes-against-covid-19 (accessed 24.3.2020)
[188] Hoffmann et al (2020) SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor, Cell. Available at: https://doi.org/10.1016/j.cell.2020.02.052 (accessed 9.3.2020)
[189] Zhang H et al (2020) Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. Available at: https://doi.org/10.1007/s00134-020-05985-9 (accessed 10.3.2020)
[190] Stebbing J et al (2020) COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis 2020. Available at: https://doi.org/10.1016/S1473-3099(20)30132-8 (accessed 5.3.2020)
[191] Ibid Harrison C (2020)
[192] Favalli et al (2020) Baricitinib for COVID-19: a suitable treatment? Available at: https://doi.org/10.1016/S1473-3099(20)30262-0 (accessed 7.4.2020)
[193] Pharmaceutical Technology (2020) Pfizer identifies lead coronavirus drug candidate. April 10, 2020. Available at: https://www.pharmaceutical-technology.com/news/pfizer-identifies-lead-coronavirus-drug-candidate/ (accessed 13.4.2020)
[194] Pharmaceutical Technology (2020) OncoImmune gets approval to trial CD24Fc for Covid-19 in US. April 9, 2020 https://www.pharmaceutical-technology.com/news/oncoimmune-covid-19-therapy-trial/ (accessed 13.4.2020)
[195] Erol (2020) High-dose intravenous vitamin C treatment for COVID-19(a mechanistic approach). PrePrint Available at: https://osf.io/p7ex8/ (accessed 5.3.2020)
[196] Cheng RZ (2020) Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)? Elsevier. Available at: https://doi.org/10.1016/j.medidd.2020.100028 (accessed 1.4.2020)
[197] Zelthuis A et al (2010) Zn Inhibits Coronavirus and Arterivirus RNA Polymerase Activity In Vitro and Zinc Ionophores Block the Replication of These Viruses in Cell Culture PLoS Pathogens DOI: 10.1371/journal.ppat.1001176 Available at: https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1001176 (accessed 9.3.2020)
[198] Xue J et al (2014) Chloroquine Is a Zinc Ionophore PLoS One. 2014; 9(10): e109180. DOI: 10.1371/journal.pone.0109180. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4182877/ (accessed 11.3.2020)
[199] CBC (2020) As coronavirus spread speeds up, Montreal researchers will trial an anti-viral treatment for COVID-19 in China. February 28, 2020. Available at: https://www.cbc.ca/radio/thecurrent/the-current-for-feb-28-2020-1.5479561/as-coronavirus-spread-speeds-up-montreal-researchers-will-trial-an-anti-viral-treatment-for-covid-19-in-china-1.5480134 (Accessed 13.3.2020)
[200] Li Y et al (2020) Therapeutic Drugs Targeting 2019-nCoV Main Protease by High-Throughput Screening. bioRxiv. Available at: https://www.biorxiv.org/content/10.1101/2020.01.28.922922v2.full.pdf (accessed 24.2.2020)
[201] Liu X, Wang XJ (2020) Potential inhibitors for 2019-nCoV coronavirus M protease from clinically approved medicines. bioRxiv. Available at: https://www.biorxiv.org/content/10.1101/2020.01.29.924100v1 (accessed 24.2.2020)
[202] Zhiheng Xu et al (2020) The efficacy of convalescent plasma for the treatment of severe influenza. Available at: https://doi.org/10.1101/2020.02.20.20025593 (accessed 25.2.2020)
[203] Mair-Jenkins J et al (2015) The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. Convalescent Plasma Study Group. J Infect Dis. Jan 1; 211(1):80-90. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25030060 (accessed 29.1.2020)
[204] CNA (2020) Chinese doctors 'using plasma therapy' on COVID-19 patients. February 18, 2020. Available at: https://www.channelnewsasia.com/news/asia/chinese-doctors-using-plasma-therapy-on-covid-19-patients-12444244 (accessed 24.2.2020)
[205] Li XY et al (2020) The Keypoints in Treatment of the Critical Coronavirus Disease 2019 Patient [Article in Chinese] Zhonghua Jie He He Hu Xi Za Zhi, 43 (0), E026 2020 Available at: https://www.ncbi.nlm.nih.gov/pubmed/32111113 (accessed 4.3.2020)

[206] Arabi YM et al (2016) Feasibility of using convalescent plasma immunotherapy for MERSCoV infection, Saudi Arabia. Emerging Infect Dis 22:1554–61, Available at: http://dx.doi.org/10.3201/eid2209.151164 (accessed 28.1.2020)
[207] Straits Times (2020) Japan's largest drugmaker working to develop coronavirus treatment. March 5, 2020. Available at: https://www.straitstimes.com/asia/east-asia/japans-largest-drugmaker-working-to-develop-coronavirus-treatment (Accessed 9.3.2020)
[208] Amanat F et al (2020) A serological assay to detect SARS-CoV-2 seroconversion in humans. Available at: https://doi.org/10.1101/2020.03.17.20037713 (Accessed 20.3.2020)
[209] Guardian (2020) Coronavirus survivors' blood plasma could be used to fight infection. March 29, 2020. https://www.theguardian.com/science/2020/mar/29/coronavirus-survivors-blood-plasma-could-be-used-to-fight-infection (accessed 2.4.2020)
[210] Clinical Trials Arena (2020) Coronavirus treatment: Vaccines/drugs in the pipeline for Covid-19. March 2, 2020. February 21, 2020. Available at: https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/ (accessed 3.3.2020)
[211] Yi L et al (2004) Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. J Virol. 78(20):11334-9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15452254 (accessed 24.2.2020)
[212] Aggarwal M, Rein J (2003) Acute human immunodeficiency virus syndrome in an adolescent. Pediatrics. 112(4):e323. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14523219 (accessed 24.2.2020)
[213] Johnson RF et al (2016) 3B11-N, a monoclonal antibody against MERS-CoV, reduces lung pathology in rhesus monkeys following intratracheal inoculation of MERS-CoV Jordan-n3/2012. Virology. 490:49-58. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26828465 (Accessed 24.2.2020)
[214] Pharmaceutical Tech (2020) Coronavirus: Gilead, Purdue University explore potential treatments. January 24, 2020. Available at: https://www.pharmaceutical-technology.com/news/coronavirus-drugs-development/ (accessed 29.1.2020)
[215] Ibid GEN (2020)
[216] Liu Y, Sun W, Li J, et al (2019) Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. medRxiv. 2020:2020.2002.2017.20024166.
[217] WHO (2020) Clinical management of severe acute respiratory infection (SARI) COVID-19 disease is suspected. Interim guidance V1.2. 13 March 2020. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected (accessed 18.3.2020)
[218] Lamontagne F et al (2020) Corticosteroid therapy for sepsis: a clinical practice guideline. BMJ. 2018;362:k3284. August 10, 2018. Available at: 10.1136/bmj.k3284 (accessed 18.3.2020)
[219] Ibid Shen K et al (2020)
[220] Lu X et al (2020) Adjuvant corticosteroid therapy for critically ill patients with COVID-19. Available at: https://doi.org/10.1101/2020.04.07.20056390 (accessed 13.4.2020)
[221] Wu, C. et al (2020). Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Internal Medicine. https://doi.org/10.1001/jamainternmed.2020.0994 (accessed 21.04.2020)
[222] Tomasz C. et al (2020) Beneficial effect of corticosteroids in severe COVID-19 pneumonia: a propensity score matching analysis. medRvix 2020. doi: https://doi.org/10.1101/2020.05.08.20094755
[223] Ibid Young BE et al (2020)
[224] Lansbury LE et al (2020) Corticosteroids as adjunctive therapy in the treatment of influenza: an updated Cochrane systematic review and meta-analysis. Crit Care Med. 2020;48(2):e98-e106. DOI:10.1097/CCM.0000000000004093. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31939808 (accessed 4.3.2020)
[225] FDA (2017) ACTEMRA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125276s114lbl.pdf (accessed 20.3.2020)
[226] Zhou Y et al (2020) Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. National Science Review. National Science Review, nwaa041, Available at: https://doi.org/10.1093/nsr/nwaa041 (accessed 20.3.2020)
[227] Mehta P et al (2020) COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet. Available at: DOI: https://doi.org/10.1016/S0140-6736(20)30628-0 (accessed 20.3.2020)
[228] CAN (2020) China approves use of Roche arthritis drug for COVID-19 patients. March 4, 2020 Available at: https://www.channelnewsasia.com/news/business/china-approves-use-of-roche-arthritis-drug-for-covid-19-patients-12499492 (accessed 4.3.2020)

[229] Ibid Harrison C (2020)
[230]Physicians Weekly (2020) China approves use of Roche drug in battle against coronavirus complications
Posted by Reuters. Mar 4, 2020. Available at: https://www.physiciansweekly.com/china-approves-use-of/ (accessed 13.3.2020)
[231] A Coomes and H Haghbayan (2020) Interleukin-6 in COVID-19: A Systematic Review and Meta-Analysis. Available at: https://doi.org/10.1101/2020.03.30.20048058 (accessed 7.4.2020)
[232] Michot JM et al (2020) Tocilizumab, an anti-IL6 receptor antibody, to treat Covid-19-related respiratory failure: a case report, Annals of Oncology (2020), doi: https://doi.org/10.1016/j.annonc.2020.03.300 (accessed 20.04.2020)
[233] Zhang X. et al (2020). First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7160284/ (accessed 20.04.2020)
[234] Pharmaceutical Technology (2020) Izana starts compassionate use study of potential Covid-19 drug. April 6. 2020. Available at: https://www.pharmaceutical-technology.com/news/izana-namilumab-covid-19-study/ (accessed 13.4.2020)
[235] EUSA PHARMA (2020) Press Release. Available at: https://www.eusapharma.com/news/eusa-pharma-and-the-papa-giovanni-xxiii-hospital/ (accessed 1.4.2020)
[236] Roivant (2020) Roivant Announces Development of Anti-GM-CSF Monoclonal Antibody to Prevent and Treat Acute Respiratory Distress Syndrome (ARDS) in Patients with COVID-19. March 18, 2020. Available at: https://roivant.com/roivant-announces-development-of-anti-gm-csf-monoclonal-antibody-to-prevent-and-treat-acute-respiratory-distress-syndrome-ards-in-patients-with-covid-19/ (accessed 1.4.2020)
[237] IMAB (2020) I-Mab Biopharma Announces Development of TJM2 to Treat Cytokine Release Syndrome Associated with Severe and Critically-Ill Patients with Coronavirus Disease (COVID-19). Available at: http://www.i-mabbiopharma.com/en/article-491.aspx (accessed 1.4.2020)
[238] Pharmaceutical Technology (2020) Sanofi and Regeneron to assess Kevzara to treat Covid-19. March 11, 2020. Available at: https://www.pharmaceutical-technology.com/news/sanofi-regeneron-kevzara-covid-19/ (accessed 12.3.2020)
[239] Clinical Trials Arena (2020) Coronavirus treatment: Vaccines/drugs in the pipeline for Covid-19. March 2, 2020. February 21, 2020. Available at: https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/ (accessed 3.3.2020)
[240] Pharmaceutical Technology (2020) Tiziana Life Sciences to work on potential Covid-19 drug. March 12, 2020. Available at: https://www.pharmaceutical-technology.com/news/tiziana-covid-19-drug-development/ (Accessed 13.3.2020)
[241] Ibid GEN (2020)
[242] Medford ARL, Millar AB (2006) Vascular endothelial growth factor (VEGF) in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS): paradox or paradigm? Thorax. 2006 Jul; 61(7): 621–626. DOI: 10.1136/thx.2005.040204. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1828639/ (accessed 4.3.2020)
[243] Clinical Trials (2020) NCT04275414 Bevacizumab in Severe or Critical Patients With COVID-19 Pneumonia (BEST-CP). US National Library of Medicine. Available at: https://clinicaltrials.gov/ct2/show/NCT04275414?cond=covid&draw=2&rank=14 (accessed 3.3.2020)
[244] Clinical Trials Arena (2020) Coronavirus treatment: Vaccines/drugs in the pipeline for Covid-19. March 2, 2020. February 21, 2020. Available at: https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/ (accessed 3.3.2020)
[245] Wang R et al (2000) Apoptosis of lung epithelial cells in response to TNF-α requires angiotensin II generation de novo. Journal of cellular physiology, 185(2), 253-259. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/1097-4652%28200011%29185%3A2%3C253%3A%3AAID-JCP10%3E3.0.CO%3B2-%23 (accessed 24.2.2020)
[246] Wang L et al (2003) Potential role of apoptotic macrophages in pulmonary inflammation and fibrosis. Journal of cellular physiology, 194(2), 215-224.Available at: https://www.ncbi.nlm.nih.gov/pubmed/12494460 (Accessed 24.2.2020)
[247] Raiden S et al (2002) Nonpeptide antagonists of AT1 receptor for angiotensin II delay the onset of acute respiratory distress syndrome. Journal of Pharmacology and Experimental Therapeutics, 303(1), 45-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12235231 (accessed 25.2.2020)

[248] Gurwitz D (2020) Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res. 2020 Mar 4. DOI: 10.1002/ddr.21656. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32129518 (Accessed 10.3.2020)
[249] Zhang H et al (2020) Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. Available at: https://doi.org/10.1007/s00134-020-05985-9 (accessed 10.3.2020)
[250] Meng et al (2020) Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Available at: https://doi.org/10.1080/22221751.2020.1746200 (accessed 19.04.2020)
[251] Vaduganathan M et al (2020). Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. New England Journal of Medicine.
[252] Mancia et al (2020) Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19. May 1, 2020. DOI: 10.1056/NEJMoa2006923 (accessed 05.05.2020)
[253] Reynolds et al (2020) Renin–Angiotensin–Aldosterone System Inhibitors and Risk of Covid-19. May 1, 2020. DOI: 10.1056/NEJMoa2008975. (accessed 05.05.2020)
[254] de Abajo, Francisco JBarreira-Hernandez, D et al. (2020) Use of renin–angiotensin–aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. May 14, 2020. DOI: https://doi.org/10.1016/S0140-6736(20)31030-8. (accessed 19.05.2020)
[255] Pipeline Review (2020) APEIRON's respiratory drug product to start pilot clinical trial to treat coronavirus disease COVID-19 in China. February 26, 2020. Available at: https://pipelinereview.com/index.php/2020022673884/Proteins-and-Peptides/APEIRONs-respiratory-drug-product-to-start-pilot-clinical-trial-to-treat-coronavirus-disease-COVID-19-in-China.html (accessed 3.3.2020)
[256] Ibid GEN (2020)
[257] Junyi Guo MD , Zheng Huang MD , Li Lin MD, PhD (2020) Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease: A Viewpoint on the Potential Influence of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers on Onset and Severity of Severe Acute Respiratory Syndrome Coronavirus 2 Infection. April 1, 2020. DOI: https://doi.org/10.1161/JAHA.120.016219. (accessed 19.05.2020)
[258] Ibid GEN (2020)
[259] Chen C et al (2020) Thalidomide Combined with Low-dose Glucocorticoid in the Treatment of COVID-19 Pneumonia. Preprints 2020, 2020020395 Available at: https://www.preprints.org/manuscript/202002.0395/v1 (accessed 5.3.2020)
[260] Chen WY (2020) Comparison of pulmonary availability and anti-inflammatory effect of dehydroandrographolide succinate via intratracheal and intravenous administration. European Journal of Pharmaceutical Sciences. Available at: https://doi.org/10.1016/j.ejps.2020.105290 (accessed 4.3.2020)
[261] Mallinckrodt (2020) Mallinckrodt Evaluates the Potential Role for Inhaled Nitric Oxide to Treat COVID-19 Associated Lung
Complications, Engages with Scientific, Governmental and Regulatory Agencies. Available at: https://mallinckrodt.gcs-web.com/node/26576/pdf (accessed 23.3.2020)
[262] Fierce Biotech (2020) FDA opens up Bellerophon's gas therapy for COVID-19, stock rockets. March 20, 2020. Available at: https://www.fiercebiotech.com/medtech/fda-expands-access-to-bellerophon-s-nitric-oxide-gas-for-covid-19-lung-symptoms (accessed 23.3.2020)
[263] Biomark (2020) Press Release. Available at: http://www.biomarck.com/pipeline/ (accessed 1.4.2020)
[264] Moore HB et al (2020) Is There a Role for Tissue Plasminogen Activator (tPA) as a Novel Treatment for Refractory COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS)?. Journal of Trauma and Acute Care Surgery.
[265] Fierce Pharma (2020) Experts float Roche stroke drug Activase as potential COVID-19 therapy. March 27, 2020. Available at: https://www.fiercepharma.com/pharma/experts-suggest-roche-s-activase-as-a-potential-covid-19-drug (accessed 1.4.2020)
[266] Science Mag (2020) New York clinical trial quietly tests heartburn remedy against coronavirus. Available at: https://www.sciencemag.org/news/2020/04/new-york-clinical-trial-quietly-tests-heartburn-remedy-against-coronavirus# (accessed 28.04.2020)
[267] Yang et al (2020) New thinking in the treatment of 2019 novel coronavirus pneumonia Complementary Therapies in Clinical Practice. Available at: https://doi.org/10.1016/j.ctcp.2020.101131 (accessed 10.3.2020)
[268] Chan KW et al (2020). COVID-19: An Update on the Epidemiological, Clinical, Preventive and Therapeutic Evidence and Guidelines of Integrative Chinese-Western Medicine for the Management

of 2019 Novel Coronavirus Disease *Am J Chin Med*. 2020;1–26. DOI:10.1142/S0192415X20500378. Available at: https://pubmed.ncbi.nlm.nih.gov/32164424/ (accessed 18.3.2020)
[269] Wang Z et al (2020) Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. BioScience Trends. Available at: https://www.jstage.jst.go.jp/article/bst/advpub/0/advpub_2020.01030/_article (accessed 24.2.2020)
[270] Tao Z et al (2014) Shufeng Jiedu Capsule protect against acute lung injury by suppressing the MAPK/NF-κB pathway. Bioscience trends, 8(1), 45-51. Available at: https://www.jstage.jst.go.jp/article/bst/8/1/8_45/_article (accessed 24.2.2020)
[271] Cinatl J et al (2003) Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. The Lancet. 361(9374):2045-6. Available at: https://linkinghub.elsevier.com/retrieve/pii/S014067360313615X (accessed 24.2.2020)
[272] Chen F et al (2004) In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol. 31(1):69-75. Available at: https://www.sciencedirect.com/science/article/pii/S1386653204000551?via%3Dihub (accessed 24.2.2020)
[273] Lin S-C et al (2017) Effective inhibition of MERS-CoV infection by resveratrol BMC Infect Dis, 17 p. 144. Available at: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-017-2253-8 (accessed 29.1.2020)
[274] Müller C et al (2017) Broad-spectrum antiviral activity of the eIF4A inhibitor silvestrol against corona- and picornaviruses. Antiviral Res. 150:123–9, Available at: http://dx.doi.org/10.1016/j.antiviral.2017.12.010 (accessed 29.1.2020)
[275] CGTN (2020) Expert: Chinese medicine Lianhua Qingwen capsule proven effective for COVID-19. May 05, 2020. Available at: https://news.cgtn.com/news/2020-05-05/Expert-Lianhua-Qingwen-capsule-proven-effective-for-COVID-19-QeXiCOf18A/index.html. (accessed 12.05.2020)
[276] CGTN (2020) Beijing approves TCM drugs for COVID-19. April 16, 2020. Available at: https://news.cgtn.com/news/2020-04-16/Beijing-approves-TCM-drugs-for-COVID-19-PJWgGfRAQg/index.html (accessed 19.05.2020)
[277] WHO (2020) Tobacco Free initiative Tobacco and waterpipe use increases the risk of suffering from COVID-19. Regional Office for the Eastern Med. Available at: http://www.emro.who.int/tfi/know-the-truth/tobacco-and-waterpipe-users-are-at-increased-risk-of-covid-19-infection.html (accessed 24.3.2020)
[278] CNN (2020) How smoking, vaping and drug use might increase risks from Covid-19.March 20, 2020. Available at: https://edition.cnn.com/2020/03/20/health/coronavirus-vaping-drugs/index.html (accessed 24.3.2020)
[279] LiuW et al (2020) Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chinese Medical Journal: February 28, 2020 - Volume Publish Ahead of Print - Issue
doi: 10.1097/CM9.0000000000000775. Available at: https://journals.lww.com/cmj/Abstract/publishahead/Analysis_of_factors_associated_with_disease.99363.aspx (accessed 24.3.2020)
[280] Ibid Jin Y-H et al (2020)
[281] Fang L et al (2020). Are patients with hypertension and diabetes mellitus at an increased risk for COVID-19 infection? The Lancet Respiratory Medicine. Available at: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30116-8/fulltext (accessed 18.3.2020)
[282] Reality Check Team and BBC Monitoring (2020). Coronavirus and ibuprofen: Separating fact from fiction. March 17, 2020. Available at: https://www.bbc.com/news/51929628 (accessed 18.3.2020)
[283] Science Alert (2020). WHO Now Officially Recommends to Avoid Taking Ibuprofen For COID-19 Symptoms. March 17, 2020. Available at: https://www.sciencealert.com/who-recommends-to-avoid-taking-ibuprofen-for-covid-19-symptoms (accessed 18.3.2020)
[284] Sommerstein R et al (2020) Coronavirus Disease 2019 (COVID-19): Do Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers Have a Biphasic Effect?Available at: https://doi.org/10.1161/JAHA.120.016509Journal of the American Heart Association. 2020;9:e016509 (accessed 14.4.2020)
[285] Bean D et al (2020) Treatment with ACE-inhibitors is associated with less severe disease with SARS-Covid-19 infection in a multi-site UK acute Hospital Trust Available at: https://doi.org/10.1101/2020.04.07.20056788 (accessed 13.4.2020)
[286] Ibid Jin Y-H et al (2020)

[287] WHO (2020) Clinical management of severe acute respiratory infection (SARI) COVID-19 disease is suspected. Interim guidance V1.2. 13 March 2020. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected (accessed 18.3.2020)
[288] Ibid Jin Y-H et al (2020)
[289] Alshahrani MS et al (2018) Extracorporeal membrane oxygenation for severe Middle East respiratory syndrome coronavirus Ann Intensive Care, 8 , p. 3, 10.1186/s13613-017-0350-x. Available at: https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-017-0350-x (accessed 29.1.2020)
[290] Schultz MJ et al (2017) Current challenges in the management of sepsis in ICUs in resource-poor settings and suggestions for the future. Intensive Care Med 2017;43:612-24
[291] WHO (2020) Clinical management of severe acute respiratory infection (SARI) COVID-19 disease is suspected. Interim guidance V1.2. 13 March 2020. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected (accessed 18.3.2020)
[292] WHO (2020) Clinical management of severe acute respiratory infection (SARI) COVID-19 disease is suspected. Interim guidance V1.2. 13 March 2020. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected (accessed 18.3.2020)
[293] Ibid Jin Y-H et al (2020)
[294] Studies cited in: Mo Y, Fisher D (2016) A review of treatment modalities for Middle East Respiratory Syndrome. J Antimicrob Chemother 71:3340–50. DOI: http://dx.doi.org/10.1093/jac/dkw338. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27585965 (accessed 28.1.2020)
[295] Zhou N, Pan T, Zhang J et al (2016) Glycopeptide antibiotics potently inhibit cathepsin L in the late endosome/lysosome and block the entry of Ebola virus, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). J Biol Chem 2016; 291: 9218–32. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26953343 (accessed 29.1.2020)
[296] Jean et al (2020) Treatment options for COVID-19: the reality and challenges. Available at: https://doi.org/10.1016/j.jmii.2020.03.034 (accessed 7.4.2020)
[297] Wang J. (2020) Efficacy and Safety of Antibiotic Agents in Children with COVID-19: A Rapid Review. DOI: https://doi.org/10.1101/2020.04.13.20064402 (accessed 21.04.2020)
[298] WHO (2020) Clinical management of severe acute respiratory infection (SARI) COVID-19 disease is suspected. Interim guidance V1.2. 13 March 2020. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected (accessed 18.3.2020)
[299] Ibid Jin Y-H et al (2020)
[300] Ibid Jin Y-H et al (2020)
[301] Ibid Jin Y-H et al (2020)
[302] WHO (2020) A coordinated Global Research Roadmap. Available at: https://www.who.int/blueprint/priority-diseases/key-action/Roadmap-version-FINAL-for-WEB.pdf?ua=1 (accessed 18.3.2020)
[303] Pang J et al (2020) Review Potential rapid diagnostics, vaccine and therapeutics for 2019 novel coronavirus (2019-nCoV): A systematic review. Journal of Clinical Medicine (in press)