Current Knowledge on the Pathogenesis of and Therapeutic Options against SARS-CoV-2: An Extensive Review of the Available Evidence

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Authors’ contributions

This work was carried out in collaboration among all authors. Author OAA designed the study. All authors participated equally in the literature search and the drafting of the initial manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: By May 16, 2020, the SARS-CoV-2 virus had spread to 188 countries, infecting over 4.6 million people and causing 310,520 fatalities. A major factor responsible for the voracious spread of the virus is the lack of specific therapeutics for treatment. Current efforts have focused on repurposing existing agents with proven antiviral properties for the treatment of SARS-CoV-2. In this review, we discuss the pathogenesis of the virus; the current standard of care and state of knowledge on the antiviral effect of some of the therapeutic options, including Chloroquine/Hydroxychloroquine, Remdesivir, Lopinavir/Ritonavir combination and Convalescent Plasma; and examine the efforts so far towards the development of a vaccine candidate against SARS-CoV-2.

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Main Body: The current standard of care which includes supportive treatment and oxygen therapy are crucial in the treatment of SARS-CoV-2 infection. Convalescent plasma has a strong immunotherapeutic potential for the treatment of both MERS-CoV and SARS-CoV infections, which many clinical studies have shown to be applicable for treating SARS-CoV-2. Remdesivir (GS-5734), an experimental Ebola virus drug effectively inhibited SARS-CoV-2 in-vitro and in-vivo, and has recently been given emergency use authorization by the United States Food and Drug Administration (FDA) following early signs of success in human clinical trials. The therapeutic potential of the Lopinavir/Ritonavir combination has been extensively explored, and though promising; it had no significant effect on viral clearance and has been associated with severe adverse reactions. Chloroquine & Hydroxychloroquine have been shown to effectively inhibit the infection in-vitro and in animal models, and had a significant viral clearance. Most vaccine development efforts remain in Phase I stage of development.

Conclusion: The current state of knowledge about the therapeutic options against SARS-CoV-2 shows great promise, however, more structured clinical studies are needed to provided much needed evidence to support the establishment of proper guidelines of therapy to curb the pandemic.

Keywords: SARS-CoV-2; COVID-19; 2019-nCoV; coronaviruses; clinical trial; therapy.

ABBREVIATIONS

| Acronym | Definition                                      |
|---------|------------------------------------------------|
| WHO     | World Health Organisation                      |
| SARS-COV| Severe Acute Respiratory Syndrome Coronavirus   |
| SARS-CoV-2| Severe Acute Respiratory Syndrome Coronavirus 2 |
| MERS-COV| Middle East Respiratory Syndrome Coronavirus   |
| β-COV   | beta Coronavirus                                |
| ORF     | Open Reading Frame                             |
| ARDS    | Acute Respiratory Distress Syndrome            |
| ECMO    | Extracorporeal Membrane Oxygenation             |
| ADE     | Antibody Dependent Enhancement                 |
| ACE-2   | Angiotensin Converting Enzyme 2                |
| CT      | Computed Tomography                             |
| CFR     | Case-Fatality Ratio                             |
| Nabs    | Neutralizing Antibodies                         |
| RDV     | Remdesivir                                     |
| EVD     | Ebola Virus Disease                             |
| LPV     | Lopinavir                                      |
| LPV/R   | Lopinavir/Ritonavir Combination                 |
| MOI     | Multiplicity of Infection                      |
| SAO₂    | Arterial Oxygen Saturation                      |
| PAO₂/FIO₂| Ratio of Partial Pressure of Oxygen to Percentage of Inspired Oxygen |
| CQ      | Chloroquine                                     |
| HCQ     | Hydroxychloroquine                              |
| SLE     | Systemic Lupus Erythematosus                    |

1. INTRODUCTION

In December 2019, a cluster of novel pneumonia cases were reported in people who had come in contact with the Huanan Seafood Wholesale Market in Wuhan, Hubei Province, China [1]. At this point, the cause of this pneumonia was said to be unknown, however, on January 7, 2020, it was confirmed to be associated with a novel strain of human coronavirus called: Severe Acute Respiratory Syndrome – Coronavirus – 2 (SARS-CoV-2) or 2019-novel coronavirus (2019-nCoV) [2]. By January 30, 2020, the outbreak was declared a Public Health Emergency of International Concern (PHEIC) and on February 11, 2020, the respiratory illness caused by the virus was named the new coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) [3]. By March 11, 2020, the WHO elevated the disease to the level of a pandemic [4], and according to data from the Johns Hopkins University Centre for Systems
Science and Engineering (CSSE) Global COVID-19 map, as at May 16, 2020, the virus had spread to 188 countries and territories, infecting over 4.6 million people and causing 310,520 fatalities [5].

A major factor responsible for the voracious spread of the virus thus far is the lack of approved therapeutic agents for the treatment of SARS-CoV-2 as well as the other two coronaviruses causing disease in humans: the SARS-CoV and the Middle East Respiratory Syndrome – Coronavirus (MERS-CoV). Apart from general supportive care, the hallmark of which involves respiratory support in form of oxygen supply for mild cases, and extracorporeal membrane oxygenation for severely ill patients, the search is still on for specific antiviral agents [6]. The process of developing new therapeutic agents is often very tedious, being required to scale several stages of laboratory, clinical and regulatory hurdles, over a period of many months to years. In a recent study, Wong et al. [7] established a success rate of 14% for experimental drug candidates in clinical trials. The urgency of the situation presented by the SARS-CoV-2 outbreak makes this impractical to curtailing the fast-spreading pandemic, thus encouraging researchers to look into the possibility of repurposing existing antiviral drugs or those already in the latter stages of development for treatment of other infections such as: hepatitis B virus (HBV), hepatitis C virus (HCV), HIV and influenza [8], taking into account similar steps conducted for the two other known human coronaviruses: SARS-CoV and MERS-CoV.

![Literature search methodology chart](image)

**Fig. 1. Literature search methodology chart**
In this review, we discuss the pathogenesis of the 2019-nCoV; highlight the current standard of care and evaluate the current state of knowledge on the antiviral effect of five of the most promising therapeutic options against SARS-CoV-2 including Chloroquine & Hydroxychloroquine, Remdesivir, Lopinavir & Ritonavir, Interferons and Convalescent Plasma. Finally, we examine the efforts taken so far towards the development of a vaccine candidate for COVID-19. We searched for relevant papers on PubMed Central, Google Scholar and HINARI using the keywords: “COVID-19”, “2019-nCoV”, “SARS-CoV-2”, “novel coronavirus disease”, “SARS-CoV”, “Drug”, “Treatment”, “Management”, “Therapeutic”, “Therapy”, “Vaccine” and “Clinical trial”. Our search generated 101 results on PubMed Central, 940 results on Google Scholar and 322 results on HINARI, making a total of 1,363 results. After screening the topics and abstracts of the results from the database, we identified 202 articles relevant to our search. 14 duplicates were then excluded giving us a total of 188 articles assessed for eligibility, 12 articles obtained from a manual search were included, making a total of 200 articles considered for the review (Fig. 1). In order to obtain the latest information on our subject of interest, we included review articles, systematic reviews, meta-analysis and clinical trials (including those retrieved from pre-print servers) of potential drugs and vaccine used for the treatment of COVID-19 in this review. Through our work, we aim to answer the question of where we are in the search for the treatment for the rapidly evolving pandemic by exploring in vitro and in vivo experiments as well as clinical trials that have been conducted and published till date.

2. PHYLGENY, VIRION, PHYSIOCHEMICAL PROPERTIES AND PATHOGENESIS OF SARS-COV-2: WHAT DO WE KNOW?

2.1 Phylogeny and Virion Characteristics

Unbiased sequencing and evolutionary tree analysis of the first isolate of SARS-CoV-2 obtained from the bronchoalveolar lavage fluid of the earliest patients of the outbreak in Wuhan, revealed that the virus was a member of the β-CoVs [9]. Generally speaking, the beta-coronaviruses are a class of enveloped, positive-sense, single-stranded RNA viruses known to cause respiratory, hepatic, digestive and neurologic diseases in humans and other animals [10,11]. The family is organized into four sub-families: α-, β-, γ-, and δ-CoVs, however, only members of the α- and β-CoVs sub-families have been known to cause diseases in humans [10,11]. As earlier stated, SARS-CoV-2 is a member of the β-CoVs, so is SARS-CoV and MERS-CoV [10]. Whole-genome phylogenetic analysis within the sub-family reveals that SARS-CoV-2 has a 79.6% sequence similarity with SARS-CoV, and a 50% similarity with MERS-CoV [9,12,13]. With a genome length of 29,900 basepairs, the SARS-CoV-2 virion (Fig. 2) has a nucleocapsid composed of the viral RNA and capsid, all embedded within a phospholipid bilayer, covered with two different types of spike proteins [14]. The first spike glycoprotein trimmer is shared by all sub-families of coronaviruses, while the second protein known as hemagglutinin-esterase is only found in a few members of the family [14]. The genome of SARS-CoV-2 has a 5’ end with a terminal sequence of 265 nucleotides, and a 3’ end with a terminal sequence of 229 nucleotides, a feature common to all β-CoVs, with a gene order 5’-replicase ORF1ab-Spike (S, 3822nt)-envelope (E, 228nt)-membrane (M, 669nt)-Nucleocapsid (N, 1260nt)-3’ [15]. Fig. 3 depicts the relative locations of each gene within the genome of SARS-CoV-2. Other predicted non-coding Open Reading Frames (ORFs) include ORF3ab, ORF6, ORF7ab, ORF8, ORF9ab and ORF10 [15].

2.2 Physiochemical Properties

Most of what we know about the physiochemical properties of SARS-CoV-2, were derived from our previous knowledge from SARS-CoV and MERS-CoV. SARS-CoV-2 is denatured by most disinfectants including: diethyl ether, 75% ethanol, chloroform, chlorine and peracetic acid, and is inactivated by ultraviolet light, or by heating at 56°C for 30 minutes [16]. Van Doremalen et al. [17], reported that SARS-CoV-2 demonstrated a higher degree of stability on plastic and stainless steel surfaces than on copper and cardboard surfaces, with viable viral copies being detectable on plastic and stainless steel up to 72 hours after application of the virus to these surfaces.
Transmission of SARS-CoV-2 occurs majorly through respiratory droplets, person-to-person contact and potentially through feco-oral routes [16]. The virus mainly infects the mucosal epithelial cells of the upper respiratory tract, including the nasal cavity and the pharynx, and less frequently in the lower respiratory tract and the gastrointestinal mucosa, as reported by Xiao et al. [18]. Several reports of the non-respiratory manifestations of SARS-CoV-2 have been published. Cheng et al. [19] reported the association between kidney impairment and death in COVID-19 patients; Guan et al. [20] reported acute liver injury in patients infected by SARS-CoV-2; while in their retrospective analysis of 138 hospitalized COVID-19 patients, Wang et al. [21] described cardiac and enteric complications in their study population; Fan et al. [22], also reported evidence that SARS-CoV-2 could cause testicular dysfunction. All these evidences point to the fact that COVID-19 may very well cause multi-system organ dysfunction.

Human angiotensin converting enzyme 2 (ACE2) is a receptor broadly expressed in the cells of the nasal mucosa, trachea, bronchus, lungs, esophagus, heart, kidney, stomach, ileum, bladder and frankly anywhere else SARS-CoV-2 has been found to infect [23], and is used by the virus to infect the target cells [24]. Asides from its role in the conversion of Angiotensin I to Angiotensin II, the ACE2 receptor is used as a binding site for the spike (S) protein of the coronaviruses [25]. The S protein exists in a stable pre-fusion state with two sub-units namely: S1 and S2. The process of binding to the ACE2
The most severe cases of human SARS-CoV-2, SARS-CoV and MERS-CoV infections often result in Acute Respiratory Distress Syndrome (ARDS), a life-threatening clinical condition characterised by a severe diminution of gas exchange in the lungs [27]. Such individuals often require various forms of respiratory support, ranging in severity from oxygen supply to mechanical ventilation and extracorporeal membrane oxygenation (ECMO). Several authors have reported pathological findings consistent with ARDS in patients infected by SARS-CoV2, SARS-CoV and MERS-CoV [28,29]. In a 2013 paper, Meyer and Christie [30] described the various inflammatory cytokines released during ARDS, mediating the inflammatory response, including: interleukin-10 (IL-10), vascular endothelial growth factor (VEGF) and tumour necrosis factor (TNF), while Thompson et al. [27], in their review paper also highlighted that elevated levels of interleukin-6 (IL-6) and interleukin-8 (IL-8) were often closely associated with adverse outcome of ARDS. Ultimately, ARDS remains the leading complication and cause of death following SARS-CoV-2 infections, a finding often attributed also to the overwhelming inflammatory response that accompanies severe infection with the virus. This overwhelming inflammatory response results in the release of excessive amounts of inflammatory cytokines, a situation known as cytokine storm [15]. Several factors have been proposed to be responsible for this effect, including: rapid viral replication resulting in massive cell death, loss of pulmonary ACE2 function due to the high-jacking of the receptor by the virus and antibody-dependent enhancement (ADE) [31]. At the onset of infection, rapid viral replication results in massive shedding and death of mucosal epithelial cells as well as endothelial lining of associated blood vessels, causing vascular leakage and stimulating the production of excessive inflammatory cytokines and chemokines [32].

3. PATTERN OF PRESENTATION

A retrospective study by Huang et al. [33] published in the early days of the SARS-CoV-2 outbreak in China describes the commonest symptoms of the infection in a cohort of 41 hospitalised patients to include: fever (98%), cough (76%) and myalgia or fatigue (44%). They also reported other symptoms such as: sputum production (28%), headache (8%), haemoptysis (5%) and diarrhoea (3%). Dyspnea occurred in 55% of their patient cohort and 63% had reduced lymphocyte count, all patients developed pneumonia with atypical findings on chest Computed Tomography (CT) scans [33]. Building on this, Wang et al. [21] conducted another retrospective study of a larger cohort of 138 hospitalised SARS-CoV-2 infected patients in Wuhan, and their results agreed significantly with those obtained by Huang’s group. In their paper, they reported the commonest symptoms in their patient cohort to be: fever (98.6%), fatigue (69.6%) and dry cough (59.4%). Milder symptoms included: myalgia (34.8%), diarrhoea (10.1%), nausea (10.1%), and headache (9%). Dyspnea occurred in 31% of the patients, 70.3% had lymphopenia and all patients showed bilateral patchy opacities or ground glass opacities of atypical pneumonia on chest CT [21]. Based on severity, 80% of individuals with SARS-CoV-2 infection will have mild to moderate (pneumonia - and non-pneumonia-associated) illness while 13.8% will have severe disease characterised by dyspnea (with respiratory rate >30 cycles/minute), PaO₂ <93% and PaO₂/FiO₂ ratio <300, while 6.1% would be critical, having severe complications such as septic shock, respiratory failure and multiple organ failure/dysfunction [34]. Asymptomatic infections have also been reported. In the Diamond Princess cruise ship outbreak in Japan, 51% of individuals with laboratory confirmed SARS-CoV-2 infection were asymptomatic at the time of testing [35]. In Japan, as of April 6, 2020, 9.3% of laboratory confirmed cases were without symptoms as well [36], while an European Centre for Disease Control (ECDC) report placed the proportion of asymptomatic cases in Italy at 44% [37] as at March 12, 2020. Based on data from China however, the Joint WHO-China International Mission indicates that about 75% of asymptomatic cases eventually progress into clinical disease [34]. Case fatality differs significantly across geographical regions. Available data on case-fatality ratio (CFR) for China, Italy and South Korea was 2.3%, 2.8% and 0.5% respectively across all age groups [37].
but was highest among those above 80 years of age – 14.8% [38], 8.2% [39] and 3.7% [40] respectively in the 3 countries.

4. CURRENT STANDARD OF CARE

According to the rapid diagnosis and treatment guideline for SARS-CoV-2 infection, developed by Jin et al. [41], the hallmark of treatment of SARS-CoV-2 infection is mainly supportive. Symptomatic patients may require bed rest with frequent monitoring of vitals with fluid resuscitation to correct electrolyte and acid-base imbalances. Some ancillary investigations that are often required include C-reactive protein (often elevated), organ function tests such as: liver enzymes, bilirubin, cardiac enzymes, electrolyte/urea/creatinine, arterial blood gas and chest imaging. Patients may also require oxygen therapy, which may be administered via: nasal catheter, oxygen mask, high-flow nasal oxygen therapy (HFNO), non-invasive ventilation (NIV) or invasive mechanical ventilation [41]. Oxygen therapy is often administered to patients with severe pneumonia, in respiratory distress, with signs of hypoxia, hypoxemia and/or shock. Extracorporeal Membrane Oxygenation (ECMO) is considered in patients whose hypoxemia is not corrected by the afore-mentioned methods.

Another hallmark of treatment involves antibiotic therapy, due to the possibility of superimposed bacterial infection (bacterial pneumonia). Generally a combination of broad spectrum antibiotics therapy is avoided due to the potential of antibiotic resistance. Routine microbial culture and sensitivity should be performed to identify the appropriate antibiotics to be used when secondary bacterial infections occur. In the absence of such laboratory facilities, empirical antibiotics treatment may be commenced using agents effective against community-acquired pneumonia, such as: amoxicillin, azithromycin and fluoroquinolones [41]. Corticosteroid therapy may be indicated in cases of severe ARDS; however their use is controversial, and approached with a great deal of caution. Studies on SARS management strategies have provided ample evidence to suggest that a combination of non-invasive continuous positive airway pressure (CPAP) and Methylprednisolone is effective for improving clinical symptoms of SARS patients, reduce disease progression and encourage absorption of lung lesions; however, it has not been able to shorten hospital stay [41]. It has also been associated with certain severe adverse effects [42] and a recent systematic review by Russell et al. [43] established that clinical evidence did not support the use of corticosteroids treatment for SARS-CoV-2 induced lung injury. In addition, the interim guidance from the WHO on the treatment of SARS due to COVID-19 advises against the use of corticosteroids unless another indication can be established [44].

Other treatment procedures include: symptomatic treatment of fever (temperature >38.5°C) using ibuprofen till a target temperature of 38°C is reached; nutritional support; use of H2 receptor antagonists and proton pump inhibitors for treatment of stress ulcers and gastrointestinal bleeding in high risk patients (risk factors include: mechanical ventilation >48 hours, liver dysfunction, renal replacement therapy and coagulopathies) and the use of low-molecular weight heparin for prophylaxis against venous embolism and other coagulopathies [41].

5. SPECIFIC THERAPEUTIC ALTERNATIVES

Currently there exists no specific antiviral agent or vaccine for the treatment of SARS-CoV-2 infection, in the past for treatment of several viral infections. It involves the use of neutralising antibody containing-plasma or sera obtained from individuals who have been infected by a particular viral pathogen but now in the convalescent phase, for the treatment of patients with active infection or for prophylaxis in high-risk individuals or those who have been exposed to the same viral pathogen. In normal individuals, viral infection stimulates a humoral immune response, which leads to the production

5.1 Convalescent Plasma and Therapeutic Neutralising Antibodies (Nabs)

Convalescent plasma treatment is a long-standing basic principle of immunotherapy that has been used in the past for treatment of several viral infections. It involves the use of neutralising antibody containing-plasma or sera obtained from individuals who have been infected by a particular viral pathogen but now in the convalescent phase, for the treatment of patients with active infection or for prophylaxis in high-risk individuals or those who have been exposed to the same viral pathogen. In normal individuals, viral infection stimulates a humoral immune response, which leads to the production
of antibodies responsible for viral neutralisation. These antibodies, known as neutralising antibodies (NAbs) are contained in the plasma, and their concentrations increase gradually as infection progresses, being highest in the convalescent phase [45] and diminishing following recovery from the infection [46]. The NAbs have two functional segments through which they elicit their protective function. The F(ab')2 fragment which is responsible for antigen recognition, by binding to portions of the antigen known as epitopes, and the crystallisable fragment Fc, which mediates immune system activation [47], and they carry out their protective function via three major steps. First, they bind through their F(ab')2 fragment to viral particles, in a way that prevents the particles from binding to their target cells, this is followed by a potent activation of the complement system or the opsonisation pathway through the Fc fragments [48]. Theoretically speaking, such a mechanism would have a potent effect in clearing viral infections and there are several historical precedents involving the use of convalescent plasma, containing NAbs in the treatment of viral infections, to prove this theory true.

In the 20th century, convalescent plasma was used in the treatment of outbreaks of measles [49,50], influenza [51] and mumps [52]. In 2006 meta-analysis by Luke et al. [53] on the use of convalescent plasma in treating patients during the 1918 Spanish flu pandemic, they proved that there was indeed a lower case-fatality rate among patients who received convalescent plasma treatment as compared with those who didn’t. Of recent, convalescent plasma has been used in the 2009-2010 H1N1 influenza virus pandemic and the 2013 Ebola virus epidemic in West Africa. Hung et al. [54], reported that patients who received convalescent plasma treatment during the 2009 H1N1 influenza virus pandemic had a significantly lower mortality rate (20% against 54.8%) as against those who did not receive the treatment. Similarly, a study conducted in Sierra Leone revealed that Ebola virus patients who were given convalescent whole blood had a higher survival rate and lower case-fatality ratio than those who received only routine treatment [55]. More evidence can be found on the successful use of convalescent plasma in the treatment of the H5N1 influenza virus outbreak [56,57] and H7N9 avian flu outbreak [58], as well as the 2003 SARS-CoV [59,60] and 2012 MERS-CoV [61] outbreaks, adding further credence to the point that convalescent plasma is indeed an effective treatment alternative for viral infections.

It is believed that NAbs to SARS-CoV-2 would act via a mechanism similar to those of SARS-CoV, given their phylogenetic similarities, and the fact that they make use of the same ACE-2 receptor for cell entry. This mechanism involves binding to the S2 subunit of the virion S protein, with which it normally binds to the receptor binding domain (RBD) of the ACE-2 receptor for cell entry [62]. By so doing, the NAbs are able to prevent the entry of the viral particles into the host cell. While several NAbs targeting the S1 subunit of SARS-CoV have been identified, such as: 80R [63], CR3014 [64], CR3022 [65], m396 [66], 201 [67,68] and B1 [69], a few antibodies with affinity for the S2 subunit have also been identified [70], suggesting an alternative mechanism for antibody-mediated viral neutralisation. Eventually viral clearance is achieved through opsonisation or complement activation [48]. There are several possible sources of antibodies against SARS-CoV-2, including: human convalescent plasma from individuals recovering from COVID-19 as well as monoclonal antibodies (mAbs) generated in animal models or through recombinant techniques. NAbs against SARS-CoV are potential alternatives as well, according to a recent letter by Tian et al. [71], which showed that CR3022 [65] demonstrated potent binding with the 2019-nCoV spike protein. However, the most readily available option is convalescent plasma obtained from recovering or recently recovered COVID-19 patients and this has been used in the few clinical trials conducted so far.

In a case series of 5 critically ill patients with confirmed SARS-CoV-2 infection and ARDS, administration of convalescent plasma resulted in marked clinical improvement of all 5 patients [72]. All 5 patients were receiving mechanical ventilation prior to the treatment and following the transfusion, body temperature of 4 out of 5 patients normalised within 3 days, the sequential organ failure assessment (SOFA) score decreased, PaO2/FiO2 also increased within 12 days (172-275 before and 284-366 following treatment), viral loads were negative in all patients within 12 days and ARDS resolved in 4 patients, while 3 were weaned off mechanical ventilation within 2 weeks [72]. In a larger clinical trial involving 19 patients, ten patients received 200 mL of convalescent plasma containing neutralising antibody with titres above 1:640 in addition to supportive care and antiviral therapy.
While the other 9 patients did not receive the convalescent plasma [73]. Three days following convalescent plasma administration, the clinical symptoms and laboratory parameters of the test patients improved markedly compared with the control. There was an increase in oxyhemoglobin saturation, lymphocyte count (0.65 x 10^9/L against 0.76 x 10^9/L) and decreased C-reactive protein (55.98 mg/L against 18.13 mg/L), radiology showed an absorption of lung lesions within 7 days and viral load was undetectable in 7 patients. Two patients were weaned off mechanical ventilation to high-flow nasal cannula, while one patient previously on high-flow nasal cannula was discontinued from oxygen therapy [73]. These two clinical studies show that convalescent plasma therapy so far may useful in the treatment of SARS-CoV-2 infection, however they do not provide evidence on its effectiveness as a stand-alone therapy as both studies have the patients also receiving other forms of treatment such as antiviral drugs and Methylprednisolone.

There are some important considerations of note concerning effective convalescent plasma therapy. First, being an example of passive antibody therapy, convalescent plasma is more effective when used for prophylaxis or shortly after the onset of symptoms, than much later [74]. This important consideration reflects in the results obtained by the trial conducted by Duan et al. [73], in which patients treated before 14 days post onset of illness (dpoi) showed better clinical and laboratory improvement compared with those treated after 14 days. Second, cocktails of NAbs showed greater efficacy for viral neutralisation than single NAbs in Ebola and SARS viruses cases [70,75]. This was explained to be probably due to the synergistic effect of different antibodies that bind to different sites of the viral particles, thus decreasing the probability that the viral particles can escape with decreased sensitivity to neutralisation [76]. In addition, Jawhara explains that for maximal efficacy, convalescent plasma obtained from patients living in the same city as those who would receive the transfusion, should be used [77]. This is because antibodies obtained from a different location may prove ineffective as other factors such as lifestyle, diet and the environment often play a significant role in the development of neutralising antibodies. Also the possibility of different viral strains across geographical regions cannot be ruled out.

Convalescent plasma therapy is not without its risks, one of which is the risk of transfusion reactions and the transmission of other infectious diseases contained in the transfused plasma. This however can easily be circumvented by standard screening protocols guiding the transfusion of blood and blood products. Another risk is that of transfusion related acute lung injury (TRALI) often occurring in critically ill individuals [78,79]. Another risk is the phenomenon of antibody-dependent enhancement (ADE), in which antibodies to one coronavirus could enhance infection to another viral strain, as described by Wan et al. [80]. However, as the proposed use of convalescent plasma relies on the use of sera with high antibody titres for the same virus – SARS-CoV-2, ADE may be unlikely and available evidence lends credence to this, as studies conducted thus far have recorded no adverse reactions [72,73].

5.2 Remdesivir (GS-5734)

Remdesivir (RDV) is a trial drug originally developed by Gilead Sciences Inc. to be used for treating the Ebola Virus Disease (EVD) [81]. It has since been shown to have broad spectrum antiviral activity against a number of RNA viruses both in vitro and in animal models. In a Nature report published by Sheahan et al. [82], they demonstrated that a combination of RDV and Interferon-ß had a superior antiviral activity over the Lopinavir, Ritonavir and interferon-ß combination therapy, against MERS-CoV strains in vitro. In addition, they showed that both prophylactic and therapeutic application of RDV was able to improve pulmonary function and decrease viral loads in MERS-CoV mice models [82]. Its efficacy against SARS-CoV has also been demonstrated both in vitro, and in mouse models [83] and in 2018, Agostini et al. [84] demonstrated that the susceptibility of both human coronaval strains to GS-5734 was mediated by viral polymerase and the proofreading exonucleases.

Remdesivir (GS-5734) is a monophosphoramidate pro-drug of the Remdesivir triphosphate (RDV-TP), a C-adenosine nucleoside analogue that acts as an inhibitor of RNA-dependent RNA polymerase, an enzyme critical to the RNA viral replication process [84,85]. Remdesivir-TP competes with adenosine triphosphate (ATP) for incorporation into the growing nucleotide chain. The selectivity value for RDV-TP suggests that its incorporation into the nucleotide chain occur through a more
effective process than for ATP and thus, following its incorporation, it triggers an abrupt termination of RNA synthesis at a position 3 nucleosides away [85]. It has been suggested that the addition of these 3 nucleotides possibly protects the RDV-TP from being cleaved by the viral 3'-5' exonucleases activity [85].

In a recent letter, Wang et al. [86] revealed that Remdesivir was an effective inhibitor of SARS-CoV-2 in vitro, using vero E6 cells, at a multiplicity of infection (MOI) of 0.05, a half-maximal effective concentration (EC50) of 0.77 μM, a half-cytotoxic concentration (CC50) greater than 100 μM and selective index (SI) greater than 129.87. They also showed that RDV had the ability to inhibit SARS-CoV-2 infection in human liver cancer Huh-7 cells, which have been shown to possess the ACE-2 receptor used by SARS-CoV-2 for cell entry [12]. In a report of the first case of SARS-CoV-2 infection treated in the USA, RDV was used on compassionate basis following the continued clinical deterioration of the index patient. The administration was accompanied by an almost immediate clinical improvement of the patient, with the disappearance of bilateral lower-lobe rales seen on chest radiograph, with no adverse effects [87]. On the human clinical trial front, Remdesivir has produces mixed results. The first human clinical trial testing the efficacy of the drug for use against SARS-CoV-2, published by the WHO showed that there was no difference between patients who received Remdesivir and those who received placebo, in terms of recovery time and mortality [88]. Further, the trial results also showed that Remdesivir administration was stopped in 11.6% of patients in the trial due to the drug’s adverse effects. These results contradict 2 other trial results, one by Gilead and the other by the National Institute of Health (NIH). In the Gilead phase 3 trial, they noted that 50% of participants had a time to clinical improvement of 11 days following Remdesivir administration [89], while in the NIH trial known as the Adaptive COVID-19 Treatment Trial (ACTT), preliminary results indicated that patients who received Remdesivir, had a 31% faster recovery time, compared with those who received placebo [90]. It was in light of this encouraging results that Remdesivir received emergency use authorisation from the Food and Drug Administration (FDA) for use in treating SARS-CoV-2 infections [91]. Interestingly, the findings of another randomized, double-blind, placebo-controlled trial in China, published in The Lancet on the same day the preliminary findings of the NIH trial were announced, significantly contradicted the NIH results. In their report, Wang et al. [92], noted that Remdesivir use was not associated with a difference in time to clinical improvement, compared with placebo. They also noted that Remdesivir was stopped in 12% of patients in the Remdesivir group, as against 5% in the placebo group [92].

In spite of the anecdotal evidence suggesting that GS-5734 may indeed be safe and effective against SARS-CoV-2, there is a need for more randomised, controlled clinical trials to settle some of the ambiguities and contradictions of those conducted till date. A search on ClinicalTrials.gov, with the keywords "COVID-19" and "Remdesivir" yielded ten results, of which nine were active trials relevant to the search parameters [93].

5.3 Lopinavir/Ritonavir

Lopinavir (LPV) is an aspartate protease inhibitor developed to be used as a treatment drug for the human immunodeficiency virus (HIV) type I. It has also been reported by several studies to exhibit efficacy in the treatment of human coronaviruses. Theoretically speaking however, this is questionable because while Lopinavir is an aspartate-like protease inhibitor, SARS-CoV and MERS-CoV possess cysteine-like proteases while the SARS-CoV-2 possesses both 3-chymotrypsin-like and papain-like proteases [94]. In addition, the HIV protease inhibitors such as Lopinavir are designed to fit into the C2 symmetry of the catalytic site of the HIV protease dimmer, a configuration that is missing in the proteases of the human coronaviruses, presenting a significant challenge to binding and efficacy [94]. In spite of these theoretical setbacks however, several reports have shown LPV to have some efficacy against SARS-CoV [95–97] and MERS-CoV [98] both in vitro and in vivo. In these studies, LPV is often used together with another agent called Ritonavir, in a Lopinavir/Ritonavir (LPV/r) combination. Ritonavir helps to increase the plasma half-life and bioavailability of LPV, by inhibiting the cytochrome P4503A (CYP3A) mediated metabolism of LPV [99].

In a unique case series reported by Wang et al. [100] involving the treatment of a cohort of four SARS-CoV-2 infected patients using a combination of LPV/r (400 mg Lopinavir/100 mg
Ritonavir), arbidol and Shufeng Jiedu Capsule (SFJDC), a traditional Chinese medicine, in addition to supportive care, three patients showed significant improvement in their clinical symptoms and laboratory parameters, two of whom were confirmed SARS-CoV-2 negative and had been discharged by the end of the study period, and the last patient showing significant improvement as well. This study provides evidence that LPV/r may be beneficial in the treatment of symptomatic SARS-CoV-2 infections. However, due to the combination of other antiviral drugs and treatment modalities, it is difficult to assess how much of the improvement was in fact due to LPV/r.

In the earlier days of the SARS-CoV-2 outbreak, Cao et al. [99] launched an urgent open-label randomised, controlled clinical trial to test the safety and efficacy of LPV/r combination for the treatment of hospitalised COVID-19 patients in Wuhan. Their cohort of 199 patients involved 99 test subjects and 100 control subjects. All patients were recruited on the basis of having a SaO₂ <94% in ambient air and a ratio of PaO₂/FiO₂ <300mmHg. The test subjects received the LPV/r combination (400mg LPV and 100mg Ritonavir) in addition to standard care for 14 days, while the control subjects received standard care alone [99]. Unfortunately, the results of the trial were disappointing as concerning its primary end point, which was the time to clinical improvement of the patients, with both groups requiring a median of 16 days [99], however, the results for the secondary end points were quite interesting.

First, there was a slightly lower (but statistically insignificant) number of deaths among the LPV/r group (14/99 vs. 25/100), but this could be explained by the fact that the standard care group were at baseline in a slightly worse condition clinically than the LPV/r group [101]. It has also been said that the open-label nature of the trial could have left the trial susceptible to interpretation bias from the clinicians. Also, it is quite difficult to separate the effect of the LPV/r administered from that of other supportive treatments such as glucocorticoids and interferon [101]. In addition, the LPV/r combination had no significant effect on viral clearance rate, a contradiction to its mechanism of action which involves the inhibition of a protease crucial to the process of viral replication. This could be a reflection of the reduced potency of the drug as a result of its conformational mismatch being an aspartate-like protease inhibitor of HIV and not an inhibitor of the 3-chymotrypsin-like and papain-like proteases of SARS-CoV-2 [94].

There have been several other observational studies on the use of the LPV/r combination in the treatment of COVID-19 patients. In a report of the 3rd case of COVID-19 confirmed in South Korea, who received the LPV/r combination, the drug was able to reduce the viral load significantly [102]. In another case report published by Han et al. [103], involving the use of LPV/r combination together with Methylprednisolone, recombinant human interferon alfa-2b and supportive therapy, for the treatment of a case of COVID-19 in China, they reported marked clinical improvement of the patient and discontinuation of ventilator support on the 8th day of treatment. In a retrospective study comparing the efficacy of an Arbidol + LPV/r combination against LPV/r alone, in the treatment of SARS-CoV-2 infection, the authors noted that while the virus was undetectable in 75% (12 of 16) of patients who received the Arbidol + LPV/r combination, only 35% (6 of 17) of patients who received LPV/r alone demonstrated similar results [104], suggesting a possible synergistic effect of both medications.

Adverse reactions to the LPV/r combination have also been frequently reported in literature. In the trial conducted by Cao and colleagues [99], 14% of the patients receiving the LPV/r combination were unable to complete the full 14-day course of treatment due to gastrointestinal adverse reactions such as: anorexia, nausea, diarrhoea and abdominal discomfort, as well as two cases of acute gastritis. Two patients also had skin eruptions, which were self-limiting. In a case series of the first 18 COVID-19 patients to be diagnosed in Singapore, of the five patients who were given the LPV/r combination, four developed similar gastrointestinal adverse events, and only one patient was able to complete the full 14-day treatment course [105]. These adverse events offer an additional area of consideration for the use of the LPV/r combination for treating SARS-CoV-2 infections.

5.4 Chloroquine/Hydroxychloroquine

Chloroquine (CQ), a drug on the WHO list of essential medicines is world renowned for the prophylaxis and treatment of Malaria. It has also been used in the management of extra-abdominal amebiasis [106]. Hydroxychloroquine (HCQ) sulphate on the other hand is a derivative of CQ which was synthesized in 1946 by
introducing a hydroxyl group into CQ, and was proven to be 40% less toxic than its parent CQ in animal models [107], and is being used not just as an antimalaria medication but also in the treatment of SLE and Rheumatoid Arthritis [108]. First discovered as “resochin” in 1934, Chloroquine has since fallen out of favour in the treatment of malaria in many countries, due to a combination of reasons ranging from the widespread development of resistance, to concerns about its toxicity in humans [109], however, the drug has in recent times been a subject of renewed attention, following reports of its potential antiviral activity [110,111]. These reports made CQ/HCQ an immediate option for consideration against SARS-CoV-2 in the early days of the pandemic, and its efficacy has been demonstrated in several published literature.

Both CQ and HCQ are weak bases capable of increasing the pH of certain acidic intracellular organelles including endosomes (EE) and endolysosomes (EL) which are crucial for membrane fusion, a step in the process of viral cell entry [112]. In addition, it has been reported that CQ was able to inhibit SARS-CoV entry into its target cell, by interfering with the glycosylation of the ACE-2 receptors employed by the virus for entry [113]. This shows that CQ and its derivative HCQ are able to block the entry and post-entry steps of viral infection. In a recent letter, Wang et al. [86] demonstrated that CQ was able to inhibit SARS-CoV-2 infection in vitro, using Vero E6 cells, with an EC90 value of 6.90 μM, which has been achieved clinically in the plasma of rheumatoid arthritis patients receiving 500 mg of the drug [114]. In another correspondence on the efficacy of HCQ in inhibiting SARS-CoV-2 infection in vitro, Liu et al. [115] showed that HCQ had a lower 50% cytotoxic concentration (CC50) compared with that of CQ (249.50 μM vs. 273.20 μM), suggesting it is a less toxic alternative to CQ. Also they showed that apart from their effect on lysosomal fusion and ACE-2 glycosylation, both drugs also have anti-inflammatory properties [108] that helps decrease the production of cytokines, alleviating the cytokine storm often associated with SARS-CoV-2 infection and responsible for many of its adverse events such as ARDS.

In a recent trial on the safety and efficacy of HCQ treatment of COVID-19 patients, conducted in Shanghai, the authors reported no significant difference between the test (400 mg HCQ + supportive therapy) and control groups (with supportive therapy only), at any of the end points investigated [116]. In another open-label, non-randomized clinical trial on the efficacy of HCQ and azithromycin conducted in France, following the administration of 600 mg of HCQ daily, together with supportive therapy and azithromycin, at day 6 post-inclusion, 70% of the HCQ treated patients had complete viral clearance as demonstrated by RT-PCR of the nasopharyngeal swab samples, as compared with 12.5% in the control group who received only supportive therapy [117].

A search on ClinicalTrials.gov with the keywords “COVID-19”, “Chloroquine” and “Hydroxychloroquine” revealed 11 active trials investigating the use of these agents for treating SARS-CoV-2 infections [118]. By extending the search to include the Chinese clinical trials registry and the WHO international clinical trial registry platforms, the number of active trials increases to about 40, with completion dates ranging from as early as April 2020 to as late as April 2021. It is believed that the results of these trials will provide sufficient data to establish the efficacy of CQ/HCQ in treating SARS-CoV-2 infections.

5.5 Vaccine

Vaccines have been responsible for the eradication of small pox [119] and the impending eradication of polio [120] globally. Such rich pedigree makes them an indispensable force in the fight between humans and infectious diseases, being able to protect against infection, especially in those regarded as most vulnerable to the adverse events of such contagions. They are also often times regarded as one of the two cheapest methods of preventing infections, the other being good sanitation and hygiene. Relating to the SARS-CoV-2 infection, the discovery of a vaccine is to be a game changing turning point, and a push towards elimination and possible eradication of the deadly virus, by preventing new infections and creating herd immunity to control disease transmission [121].

The advantages of a vaccine go beyond an improvement of health outcomes, as described by Lu [122], but also in the stabilization of the global economy, bringing it back on track as soon as possible. Several groups have already taken up the challenge of developing an effective vaccine against SARS-CoV-2, and more entities, both private and public institutions are entering the scene, in a similar manner as during the SARS-CoV outbreak [123]. For example,
6. CONCLUSION

In conclusion, we have discussed extensively, the pathogenesis, highlighted the current standards of care and explored the current situation as regards the therapeutic options against the SARS-CoV-2. We have also examined the efforts thus far in the process of vaccine development. We have demonstrated that while the current standard of care remains the bedrock of SARS-CoV-2 therapy, there is an urgent need to identify and commission the several potential therapeutic agents under investigation, following the results of ongoing clinical investigations. This would be essential in the fight against the raging pandemic and would have a ripple effect on the push towards a quick recovery of the global economy post-pandemic. Finally, the discovery of a vaccine would be crucial towards the elimination or the possible eradication of the disease. Further understanding of the pathogenesis of SARS-CoV-2 would be instrumental in this regard.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. WHO | Pneumonia of unknown cause – China. WHO [Internet]; 2020. [cited 2020 Apr 2]; Available:https://www.who.int/csr/don/05-january-2020-pneumonia-of-unknown-cause-china/en/
2. Gorbalenya AE. Severe acute respiratory syndrome-related coronavirus – The species and its viruses, a statement of the Coronavirus Study Group. bioRxiv. 2020; 2020.02.07.937862.
3. Coronavirus (COVID-19) events as they happen [Internet]. [cited 2020 Apr 2] Available:https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen
4. Coronavirus disease (COVID-19) outbreak [Internet]. [cited 2020 Apr 2] Available:https://www.coronavirus.jhu.edu/map.html
5. COVID-19 Map - Johns Hopkins Coronavirus Resource Center [Internet]. [cited 2020 Apr 2] Available:https://www.coronavirus.jhu.edu/map.html
6. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis [Internet]. 2020;20(2):19–20. DOI:https://doi.org/10.1016/S1473-3099(20)30141-9
7. Heem Wong C, Wei Siah K, Lo AW. Estimation of clinical trial success rates and related parameters. Biostatistics [Internet]. 2019;20:273–86.
17. De Clercq E, Li G. Approved antiviral drugs over the past 50 years [Internet]. Vol. 29, Clinical Microbiology Reviews. American Society for Microbiology. 2016;695–747. [cited 2020 Apr 2]
Available: http://www.ncbi.nlm.nih.gov/pubmed/27281742

18. Weiss SR, Leibowitz JL. Coronavirus pathogenesis. In: Advances in Virus Research [Internet]. Academic Press Inc. 2011;85–164. [cited 2020 Apr 3]
Available: http://www.ncbi.nlm.nih.gov/pubmed/22094080

19. Zhou P, Yang X Lou, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–3.

20. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet. 2020;395(10224):565–74.

21. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265–9.

22. Jin Y, Yang H, Wu W, Chen S, Zhang W, Duan G. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. Viruses. 2020;12(372):1–17.

23. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 6, Revised) [Internet]; 2020. [cited 2020 Apr 3].
Available: http://www.kankyokansen.org/uploads/uploads/files/jsipc/protocol_V6.pdf

24. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med [Internet]; 2020. [cited 2020 Apr 3].
Available: http://www.ncbi.nlm.nih.gov/pubmed/32182409

25. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology [Internet]; 2020. [cited 2020 Apr 3].
Available: http://www.ncbi.nlm.nih.gov/pubmed/32142773

26. de Wilde AH, Snijder EJ, Kikker M, van Hemert MJ. Host factors in coronavirus replication. In: Current Topics in Microbiology and Immunology [Internet]. Springer Verlag. 2018;1–42. [cited 2020 Apr 3]
Available: http://www.ncbi.nlm.nih.gov/pubmed/28643204

27. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727–33.

28. Weiss SR, Leibowitz JL. Coronavirus pathogenesis. In: Advances in Virus Research [Internet]. Academic Press Inc. 2011;85–164. [cited 2020 Apr 3]
Available: http://www.ncbi.nlm.nih.gov/pubmed/22094080

29. Donoghue M, Hsieh F, Baronas E, SK, Berne MA, et al. Angiotensin converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426(6965):450–4.

30. Adesanya et al.; IJPR, 4(2): 16-36, 2020; Article no.IJPR.57256
related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circ Res. 2000;87(5).

26. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science (80-.). 2020;367(6483):1260–3.

27. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome [Internet]. Vol. 377, New England Journal of Medicine. Massachusetts Medical Society. 2017;562–72. [cited 2020 Apr 3]
Available: http://www.ncbi.nlm.nih.gov/pubmed/28792873

28. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med [Internet]; 2020. [cited 2020 Apr 3]
Available: http://www.ncbi.nlm.nih.gov/pubmed/32085846

29. Ng DL, Al Hosani F, Keating MK, Gerber SI, Jones TL, Metcalfe MG, et al. Clinicopathologic, immunohistochemical, and ultrastructural findings of a fatal case of middle east respiratory syndrome coronavirus infection in the United Arab Emirates, April 2014. Am J Pathol. 2016;186(3):652–8.

30. Meyer NJ, Christie JD. Genetic heterogeneity and risk of acute respiratory distress syndrome. Semin Respir Crit Care Med [Internet], 2013;34(4):459–74. [cited 2020 Apr 3]
Available: http://www.ncbi.nlm.nih.gov/pubmed/23934715

31. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-Mediated Inflammatory Responses: From Mechanisms to Potential Therapeutic Tools [Internet]. Virologica Sinica. Science Press; 2020. [cited 2020 Apr 3]
Available: http://www.ncbi.nlm.nih.gov/pubmed/32125642

32. Yang M. Cell Pyroptosis, a Potential Pathogenic Mechanism of 2019-nCoV Infection. SSRN Electron J; 2020.

33. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.

34. Aylward, Bruce (WHO); Liang W (PRC). Report of the WHO-China Joint mission on coronavirus disease 2019 (COVID-19). WHO-China Jt Mission Coronavirus Dis 2019 [Internet]. 2020;2019(February):16–24.
Available: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf

35. Field Briefing: Diamond Princess COVID-19 Cases, 20 Feb Update [Internet] [cited 2020 Apr 6].
Available: https://www.niid.go.jp/niid/en/2019-ncov-e/9417-covid-dp-fe-02.html

36. About Coronavirus Disease 2019 (COVID-19) [Internet]. [cited 2020 Apr 6].
Available: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/newpage_00032.html

37. European Centre for Disease Prevention and Control. Novel coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK – sixth update – 12 March 2020. Stockholm: ECDC; 2020. Novel coronavirus disease 2019 ( COVID-19 ) pandemic: increased transmission in the EU / EEA and the UK – sixth update. Rapid Risk Assess; 2020. 2019(March).

38. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) — China, 2020 [Internet]; 2020. [cited 2020 Apr 6]
Available: http://www.ourphn.org.au/wp-content/uploads/20200225-Article-COVID-19.pdf

39. Epidemia COVID-19: Aggiornamento nazionale 09 marzo 2020 – ore 16:00 [Internet]. Rome; 2020.
Available: https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorgeliazza-integrata-COVID-19_09-marzo-2020.pdf

40. Report on the epidemiological features of coronavirus disease 2019 (covid-19) outbreak in the republic of korea from january 19 to March 2, 2020. J Korean Med Sci. 2020;35(10).

41. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res. 2020;7(1):1–23.

42. Xiao J zhong, Ma L, Gao J, Yang Z jun, Xing X yan, Zhao H chuan, et al. Glucocorticoid-induced diabetes in severe acute respiratory syndrome: The impact of high dosage and duration of
methylprednisolone therapy. Zhonghua Nei Ke Za Zhi. 2004;43(3):179–82.

43. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Vol. 395, The Lancet. Lancet Publishing Group. 2020;473–5.

44. WHO. Clinical management of severe acute respiratory infection when COVID-19 is suspected (v1.2) [Internet]. Geneva; 2020. Available:https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

45. Klasse PJ. Neutralization of Virus Infectivity by Antibodies: Old Problems in New Perspectives. Adv Biol [Internet]; 2014. [cited 2020 Apr 8] Available:http://www.ncbi.nlm.nih.gov/pubmed/27099867

46. Cao WC, Liu W, Zhang PH, Zhang F, Richardus JH. Disappearance of antibodies to SARS-associated coronavirus after recovery [18]. New England Journal of Medicine. Massachussets Medical Society. 2007; 357:1162–3.

47. Galeotti C, Kaveri S V, Bayry J. IVIG-mediated effector functions in autoimmune and inflammatory diseases. Int Immunol [Internet]. 2017;29(11):491–8. [cited 2020 Apr 8] Available:http://www.ncbi.nlm.nih.gov/pubmed/2866326

48. Coughlin MM, Prabhakar BS. Neutralizing human monoclonal antibodies to severe acute respiratory syndrome coronavirus: Target, mechanism of action, and therapeutic potential. Rev Med Virol. 2012; 22(1):2–17.

49. Park WH, Freeman RG. The prophylactic use of measles convalescent serum. J Am Med Assoc. 1926;87(8):556–8.

50. Gallagher JR. Use of Convalescent Measles Serum to Control Measles in a Preparatory School. Am J Public Heal Nations Heal [Internet]. 1935;25(5):595–8. [cited 2020 Apr 8] Available:http://www.ncbi.nlm.nih.gov/pubmed/18014217

51. Luke TC, Casadevall A, Watowich SJ, Hoffman SL, Beigel JH, Burgess TH. Hark back: Passive immunotherapy for influenza and other serious infections. Crit Care Med [Internet]. 2010;38(SUPPL. 4):e66-73. Available:http://www.ncbi.nlm.nih.gov/pubmed/20154602

52. RAMBAR AC. Mumps; use of convalescent serum in the treatment and prophylaxis of orchitis. Am J Dis Child. 1946;71:1–13.

53. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: Convalescent blood products for Spanish influenza pneumonia: A future H5N1 treatment? [Internet]. Vol. 145, Annals of Internal Medicine. American College of Physicians; 2006;599–609. [cited 2020 Apr 8] Available:http://www.ncbi.nlm.nih.gov/pubmed/16940336

54. Hung IF, To KK, Lee C-K, Lee K-L, Chan K, Yan W-W, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis [Internet]. 2011;52(4):447–56. [cited 2020 Apr 8] Available:http://www.ncbi.nlm.nih.gov/pubmed/21248066

55. Sahr F, Ansumana R, Massaquoi TA, Idriss BR, Sesay FR, Lamin JM, et al. Evaluation of convalescent whole blood for treating Ebola Virus Disease in Freetown, Sierra Leone. J Infect [Internet]. 2017; 74(3):302–9. [cited 2020 Apr 8] Available:http://www.ncbi.nlm.nih.gov/pubmed/27867062

56. Kong LK, Zhou BP. Successful treatment of avian influenza with convalescent plasma [1]. Hong Kong Medical Journal. 2006;12:489.

57. Zhou B, Zhong N, Guan Y. Treatment with convalescent plasma for influenza A (H5N1) infection [9]. New England Journal of Medicine. Massachusetts Medical Society. 2007;357:1450–1.

58. Wu XX, Gao HN, Wu HB, Peng XM, Ou HL, Li LJ. Successful treatment of avian-origin influenza A (H7N9) infection using convalescent plasma. Int J Infect Dis. 2015;41:3–5.

59. Cheng Y, Wong R, Soo YOY, Wong WS, Lee CK, Ng MHL, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis [Internet]. 2005;24(1):44–6. [cited 2020 Apr 8] Available:http://www.ncbi.nlm.nih.gov/pubmed/15616839
60. Yeh K-M, Chiueh T-S, Siu LK, Lin J-C, Chan PKS, Peng M-Y, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. J Antimicrob Chemother [Internet]. 2005;56(5):919–22. [cited 2020 Apr 8]; Available: http://www.ncbi.nlm.nih.gov/pubmed/16183666

61. Ko JH, Seok H, Cho SY, Ha YE, Baek JY, Kim SH, et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory syndrome coronavirus infection: A single centre experience. Antivir Ther [Internet]. 2018;23(7):617–22. [cited 2020 Apr 8]; Available: http://www.ncbi.nlm.nih.gov/pubmed/29923831

62. Wong SK, Li W, Moore MJ, Choe H, Farzan M. A 193-Amino Acid Fragment of the SARS Coronavirus S Protein Efficiently Binds Angiotensin-converting Enzyme 2. J Biol Chem [Internet]. 2004;279(5):3197–201. [cited 2020 Apr 8]; Available: http://www.ncbi.nlm.nih.gov/pubmed/14670965

63. Sui J, Li W, Murakami A, Tamin A, Matthews LJ, Wong SK, et al. Potent neutralization of severe acute respiratory syndrome (SARS) coronavirus by a human mAb to S1 protein that blocks receptor association. Proc Natl Acad Sci U S A [Internet]. 2004;101(8):2536–41. [cited 2020 Apr 8]; Available: http://www.ncbi.nlm.nih.gov/pubmed/14983044

64. van den Brink EN, Ter Meulen J, Cox F, Jongeneelen MAC, Thijssse A, Throsby M, et al. Molecular and biological characterization of human monoclonal antibodies binding to the spike and nucleocapsid proteins of severe acute respiratory syndrome coronavirus. J Virol [Internet]. 2005;79(3):1635–44. [cited 2020 Apr 8]; Available: http://www.ncbi.nlm.nih.gov/pubmed/15650189

65. Ter Meulen J, Van Den Brink EN, Poon LLM, Marissen WE, Leung CSW, Cox F, et al. Human monoclonal antibody combination against SARS coronavirus: Synergy and coverage of escape mutants. PLoS Med [Internet]. 2006;3(7):1071–9. [cited 2020 Apr 8]; Available: http://www.ncbi.nlm.nih.gov/pubmed/16796401

66. Zhu Z, Chakraborti S, He Y, Roberts A, Sheahan T, Xiao D, et al. Potent cross-reactive neutralization of SARS coronavirus isolates by human monoclonal antibodies. Proc Natl Acad Sci U S A [Internet]. 2007;104(29):12123–8. [cited 2020 Apr 8]; Available: http://www.ncbi.nlm.nih.gov/pubmed/17620608

67. Coughlin M, Lou G, Martinez O, Masterman SK, Olsen OA, Moksa AA, et al. Generation and characterization of human monoclonal neutralizing antibodies with distinct binding and sequence features against SARS coronavirus using XenoMouse®. Virology. 2007;361(1):93–102.

68. Greenough TC, Babcock GJ, Roberts A, Hernandez HJ, Thomas, Jr. WD, Coccia JA, et al. Development and Characterization of a Severe Acute Respiratory Syndrome–Associated Coronavirus–Neutralizing Human Monoclonal Antibody That Provides Effective Immunoprophylaxis in Mice. J Infect Dis [Internet]. 2005;191(4):507–14. [cited 2020 Apr 8]; Available: http://www.ncbi.nlm.nih.gov/pubmed/15655773

69. Duan J, Yan X, Guo X, Cao W, Han W, Qi C, et al. A human SARS-CoV neutralizing antibody against epitope on S2 protein. Biochem Biophys Res Commun [Internet]. 2005;333(1):186–93. [cited 2020 Apr 8]; Available: http://www.ncbi.nlm.nih.gov/pubmed/15939399

70. Elshabrawy HA, Coughlin MM, Baker SC, Prabhakar BS. Human Monoclonal Antibodies against Highly Conserved HR1 and HR2 Domains of the SARS-CoV Spike Protein Are More Broadly Neutralizing. PLoS One [Internet]. 2012;7(11):e50366. [cited 2020 Apr 8]; Available: http://www.ncbi.nlm.nih.gov/pubmed/23185609

71. Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, et al. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus- specific human monoclonal antibody. Emerg Microbes Infect. 2020;9:382–5.

72. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 Critically Ill Patients With COVID-19 With
73. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. The feasibility of convalescent plasma therapy in severe COVID-19 patients: A pilot study. medRxiv. 2020; (8):1–22.

74. Casadevall A, Pirofski L, Casadevall A, Pirofski L. The convalescent sera option for containing COVID-19 The convalescent sera option for containing COVID-19. J Clin Invest. 2020;130(4):1545–8.

75. Davey RT, Dodd L, Proshan MA, Neaton J, Nordwall JN, Koopmeiners JS, et al. A randomized, controlled trial of ZMapp for Ebola virus infection. N Engl J Med. 2016; 375(15):1448–56.

76. Zhou G, Zhao Q. Perspectives on therapeutic neutralizing antibodies against the Novel Coronavirus SARS-CoV-2. Int J Biol Sci. 2020;16:1718–23.

77. Jawhara S. Could Intravenous Immunoglobulin Collected from Recovered Coronavirus Patients Protect against COVID-19 and Strengthen the Immune System of New Patients? Int J Mol Sci. 2020;21:2272.

78. Gajic O, Rana R, Winters JL, Yilmaz M, Mendez JL, Rickman OB, et al. Transfusion-related acute lung injury in the critically ill: Prospective nested case-control study. Am J Respir Crit Care Med [Internet]. 2007;176(9):886–91. [cited 2020 Apr 8]
Available:http://www.ncbi.nlm.nih.gov/pubmed/17626910

79. Benson AB, Moss M, Silliman CC. Transfusion-related acute lung injury (TRALI): A clinical review with emphasis on the critically ill [Internet]. Vol. 147, British Journal of Haematology. 2009;431–43. [cited 2020 Apr 8]
Available:http://www.ncbi.nlm.nih.gov/pubmed/19663827

80. Wan Y, Shang J, Sun S, Tai W, Chen J, Geng Q, et al. Molecular Mechanism for Antibody-Dependent Enhancement of Coronavirus Entry. J Virol [Internet]. 2020; 94(5). [cited 2020 Apr 8]
Available:http://www.ncbi.nlm.nih.gov/pubmed/31826992

81. Mulangu S, Dodd LE, Davey RT, Mbaya OT, Proshan M, Mukadi D, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med [Internet]. 2019;381(24):2293–303. [cited 2020 Apr 11]
Available:http://www.ncbi.nlm.nih.gov/pubmed/31774950

82. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun [Internet]. 2020;11(1):222. [cited 2020 Apr 11]
Available:http://www.ncbi.nlm.nih.gov/pubmed/31924756

83. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017;28:9(396).

84. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. MBio. 2018;9(2).

85. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem. 2020;jbc.AC120.013056.

86. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Vol. 30, Cell Research. Springer Nature. 2020;269–71.

87. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382(10):929–36.

88. Boseley S. First trial for potential Covid-19 drug shows it has no effect. The Guardian [Internet]; 2020. [cited 2020 May 17]
Available:https://www.theguardian.com/world/2020/apr/23/high-hopes-drug-for-covid-19-treatment-failed-in-full-trial

89. Gilead Sciences. Gilead Announces Results From Phase 3 Trial of Investigational Antiviral Remdesivir in Patients With Severe COVID-19 [Internet]. Press Releases; 2020. [cited 2020 May 17]
Available: https://www.gilead.com/news-and-press/press-room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-in-patients-with-severe-covid-19

90. National Institutes of Health (NIH). NIH clinical trial shows Remdesivir accelerates recovery from advanced COVID-19 [Internet]. News Releases; 2020. [cited 2020 May 17] Available: https://www.nih.gov/news-events/news-releases/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19

91. Food and drug administration (FDA). Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment [Internet]. Press Announcements; 2020. [cited 2020 May 17] Available: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment

92. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial. Lancet [Internet]. 2020;0(0):1569–78. [cited 2020 May 17] Available: https://linkinghub.elsevier.com/retrieve/pii/S0140673620310229

93. Search of: Remdesivir | COVID-19 - List Results - ClinicalTrials.gov [Internet]. [cited 2020 Apr 11] Available: https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Remdesivir&entry=&state=&city=&dist=

94. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov [Internet]. 2020; 19(March):19–20. DOI: http://dx.doi.org/10.1038/d41573-020-00016-0

95. Chu CM, Cheng VCC, Hung IFN, Wong MML, Chan KH, Chan KS, et al. Role of lopinavir/ritonavir in the treatment of SARS: Initial virological and clinical findings. Thorax. 2004;59(3):252–6. Chen F, Chan KH, Jiang Y, Kao RYT, Lu HT, Fan KW, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol [Internet]. 2004;31(1):69–75.

Available: http://www.ncbi.nlm.nih.gov/pubmed/15288617 [cited 2020 Apr 11]

96. Wu CY, Jan JT, Ma SH, Kuo CJ, Juan HF, Cheng YSE, et al. Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc Natl Acad Sci U S A [Internet]. 2004;101(27): 10012–7. [cited 2020 Apr 11] Available: http://www.ncbi.nlm.nih.gov/pubmed/15226499

97. De Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, Van Nieuwkoop S, Bestebroer TM, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrob Agents Chemother [Internet]. 2014;58(8): 4875–84. [cited 2020 Apr 11] Available: http://www.ncbi.nlm.nih.gov/pubmed/24841269

98. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020;1–13.

99. Wang Z, Chen X, Lu Y, Chen F, Zhang W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. Biosci Trends. 2020;14(1):64–8.

100. Baden LR, Rubin EJ. Covid-19 — The Search for Effective Therapy. N Engl J Med. 2020;1–2.

101. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, et al. Case of the index patient who caused tertiary transmission of coronavirus disease 2019 in Korea: The application of lopinavir/ritonavir for the treatment of COVID-19 pneumonia monitored by quantitative RT-PCR. J Korean Med Sci. 2020;35(6).

102. Han W, Quan B, Guo Y, Zhang J, Lu Y, Feng G, et al. The course of clinical diagnosis and treatment of a case infected with coronavirus disease 2019 [Internet]. Vol. 92, Journal of Medical Virology. John Wiley and Sons Inc.; 2020;461–3. [cited 2020 Apr 11] Available: http://www.ncbi.nlm.nih.gov/pubmed/32073161

103. Deng L, Li C, Zeng Q, Liu X, Li X, Zhang H, et al. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus
Chloroquine is a potent inhibitor of SARS-CoV-2 in Singapore. JAMA - J Am Med Assoc; 2020.

104. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected with SARS-CoV-2 in Singapore. JAMA - J Am Med Assoc; 2020.

105. Sodeman WA, Doerner AA, Gordon EM, Gillikin CM. Chloroquine in hepatic amebiasis. Ann Intern Med [Internet]. 1951;35(2):331–41. [cited 2020 Apr 12]; Available:http://www.ncbi.nlm.nih.gov/pubmed/14857603

106. McChesney EW. Animal toxicity and pharmacokinetics of hydroxychloroquine sulfate. Am J Med [Internet]. 1983;75(PART 1):11–8. [cited 2020 Apr 12]. Available:http://www.ncbi.nlm.nih.gov/pubmed/6408923

107. Lee SJ, Silverman E, Bargman JM. The role of antimalarial agents in the treatment of SLE and lupus nephritis [Internet]. Vol. 7, Nature Reviews Nephrology. 201;718–29. [cited 2020 Apr 12]. Available:http://www.ncbi.nlm.nih.gov/pubmed/22009248

108. Weniger H. Review of side effects and toxicity of chloroquine. Bull World Health Organ. 1979;79(906).

109. Savarino A, Di Trani L, Donatelli I, Cauda R, Cassone A. New insights into the antiviral effects of chloroquine [Internet]. Vol. 6, Lancet Infectious Diseases. Lancet Publishing Group. 2006;67–9. [cited 2020 Apr 12]. Available:http://www.ncbi.nlm.nih.gov/pubmed/16439323

110. Yan Y, Zou Z, Sun Y, Li X, Xu KF, Wei Y, et al. Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model. Vol. 23, Cell Research. 2013:300–2.

111. Mauthe M, Orhon I, Rocchi C, Zhou X, Luhr M, Hjikema KJ, et al. Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion. Autophagy [Internet]. 2018;14(8):1435–55. [cited 2020 Apr 12]. Available:http://www.ncbi.nlm.nih.gov/pubmed/29940786

112. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazeck TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005;2.

113. Mackenzie AH. Dose refinements in long-term therapy of rheumatoid arthritis with antimalarials. Am J Med. 1983;75(PART 1):40–5.

114. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov [Internet]. 2020;6(1):6–9. DOI:http://dx.doi.org/10.1038/s41421-020-0156-0

115. ChEN J, LIU D, LIU L, LIU P, Xu Q, XIA L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ (Med Sci) [Internet]. 2020;49(February):1–10. [cited 2020 Apr 12]. Available:http://www.zjujournals.com/med/EN/10.3785/j.issn.1008-5507.2020.03.03

116. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;1–24.

117. Search of: Chloroquine, Hydroxychloroquine | COVID-19 - List Results - ClinicalTrials.gov [Internet]. [cited 2020 Apr 12]. Available:https://clinicaltrials.gov/ct2/result s?cond=COVID-19&term=Chloroquine%2C%20Hydroxychloroquine&ctry=&state=&city=&dist=

118. Riedel S. Edward Jenner and the History of Smallpox and Vaccination. Baylor Univ Med Cent Proc. 2005;18(1):21–5.

119. Baicus A. History of polio vaccination. World J Virol. 2012;1(4):108.

120. Pang J, Wang MX, Ang IYH, Tan SHX, Lewis RF, Chen JI, et al. Potential Rapid Diagnostics, Vaccine and Therapeutics for 2019 Novel Coronavirus (2019-nCoV): A Systematic Review. J Clin Med [Internet]. 2020;9(3):623. [cited 2020 Apr 12]. Available:http://www.ncbi.nlm.nih.gov/pubmed/32110875

121. Lu S. Timely development of vaccines against SARS-CoV-2 [Internet]. Vol. 9, Emerging Microbes and Infections. Taylor and Francis Ltd. 2020;542–4. [cited 2020 Apr 12]. Available:http://www.ncbi.nlm.nih.gov/pubmed/32148172
123. Bijlenga G. Proposal for vaccination against SARS coronavirus using avian infectious bronchitis virus strain H from The Netherlands [7] [Internet]. Vol. 51, Journal of Infection. 2005;263–5. [cited 2020 Apr 12]
Available:http://www.ncbi.nlm.nih.gov/pubmed/16045996

124. Johnson J &. What You Need to Know About Coronavirus and a Potential Johnson & Johnson Vaccine [Internet]. [cited 2020 Apr 12].
Available:https://www.jnj.com/latest-news/what-you-need-to-know-about-coronavirus-and-a-potential-johnson-johnson-vaccine

125. Sanofi. Sanofi joins forces with U.S. Department of Health and Human Services to advance a novel coronavirus vaccine - Feb 18, 2020[Internet]. [cited 2020 Apr 12].
Available: http://www.news.sanofi.us/2020-02-18-Sanofi-joins-forces-with-U-S-Department-of-Health-and-Human-Services-to-advance-a-novel-coronavirus-vaccine

126. Zhou Z, Post P, Chubet R, Holtz K, McPherson C, Petric M, et al. A recombinant baculovirus-expressed S glycoprotein vaccine elicits high titers of SARS-associated coronavirus (SARS-CoV) neutralizing antibodies in mice. Vaccine [Internet]. 2006;24(17):3624–31. [cited 2020 Apr 12]
Available:http://www.ncbi.nlm.nih.gov/pubmed/16497416

127. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. J Med Virol [Internet]. 2020;92(5):479–90. [cited 2020 Apr 12]
Available:https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25707

128. CEPI to fund three programmes to develop vaccines against the novel coronavirus, nCoV-2019 – CEPI [Internet]. [cited 2020 Apr 12].
Available:https://cepi.net/news_cepi/cepi-to-fund-three-programmes-to-develop-vaccines-against-the-novel-coronavirus-ncov-2019/

129. Yong CY, Ong HK, Yeap SK, Ho KL, Tan WS. Recent Advances in the Vaccine Development Against Middle East Respiratory Syndrome-CoV. Front Microbiol [Internet]. 2019;10:1781. [cited 2020 Apr 12]
Available:http://www.ncbi.nlm.nih.gov/pubmed/31428074

130. Modjarrad K, Roberts CC, Mills KT, Castellano AR, Paolino K, Muthumani K, et al. Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: A phase 1, open-label, single-arm, dose-escalation trial. Lancet Infect Dis [Internet]. 2019;19(9):1013–22. [cited 2020 Apr 12]
Available:http://www.ncbi.nlm.nih.gov/pubmed/31351922

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