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## COVID-19: Where is the treatment?

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### Abstract

Even though the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is related to SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), identifying effective and safe therapeutic strategies remains challenging. In search of finding effective treatments to eradicate the virus and improve disease symptoms, scientists are exploring possible therapies such as anti-viral, anti-malaria, immune therapy, and hormone treatments. However, the efficacy of these treatments was not validated on either SARS-CoV or MERS-CoV. In this study, we have reviewed synthetic evidence achieved through systematic and meta-analysis of therapeutics specific for SARS-CoV-2 and observed that the use of the above-mentioned therapies had no clinical benefits in coronavirus disease 2019 patients and, conversely, displayed side effects.

**Key Words:** COVID-19; Meta-analysis; Therapeutics; Anti-viral drugs; Immune therapy; Corticosteroids

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**Core Tip:** The outcomes from these studies, supporting the use of anti-corona therapies, remain mostly inconclusive and uninspiring, so far, because of the lack of evidence, methodological flaws, missing data entries, risk of bias, publication bias, heterogeneity of outcomes and the number of subjects included in the respective studies. High-quality

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data from more stringent studies involving large samples, particularly randomized clinical studies, and caution on when to employ the treatments are needed.

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## INTRODUCTION

From the establishment of PRISMA guidelines in 2009, it is obvious that the importance and use of meta-analysis is growing at an unprecedented rate in scientific explorations. Meta-analysis is a statistical approach for evaluating the pooled data from various original research studies to provide quantitative, concise, and up to date knowledge[1]. Meta-analysis provides research outcomes *via* scientific synthesize through investigating the size of the effect or overall effect. This statistical analysis played a profound role in providing an evidence-based tool and in clarifying, superficially, paradoxical outcomes in several scientific domains; thus, eliminating controversy and criticism over particular study outcomes[1]. Though the term “meta-analysis” was born in the 1970s, currently the use of this tool has extended from medical sciences to other fields like physiology, conservation, evolution and ecological sciences; this infiltration strongly suggests that meta-analysis is replacing narrative reviews as an alternative, objective and instructive way of recapping biological concepts[2]. Synthesis of evidence from meta-analysis should become a common practice in order to maximize the value of scientific study in primary experimental research. Meta-analysis is very crucial to make progress in biological, medical, policy and conservation applications since these fields are greatly dependent on evidence-based outcomes[1,2]. Meta-analysis has aided in finding patterns, building projections, achieving generalizations and creating evidence-based conclusions in several research branches including oncology[3], obesity[4], pathophysiology[5], drug discovery[6] and diagnostic test accuracy[7]. Moreover, the exploration of corona virus and its therapeutic choices using meta-analysis is growing, even though the amount of original research articles over the topic are limited and these statistical outcomes are creating a corner to reach vast generalizations. Very recently, multiple meta-studies have reported their evidence-based outcomes with traditional medicines, anti-viral drugs, immune boosters, immunotherapy and use of hydroxychloroquine as treatment options in association with corona viral infection[8-12]. These meta-studies hoped to use existing evidence and provide the likability of treatment success on novel corona virus.

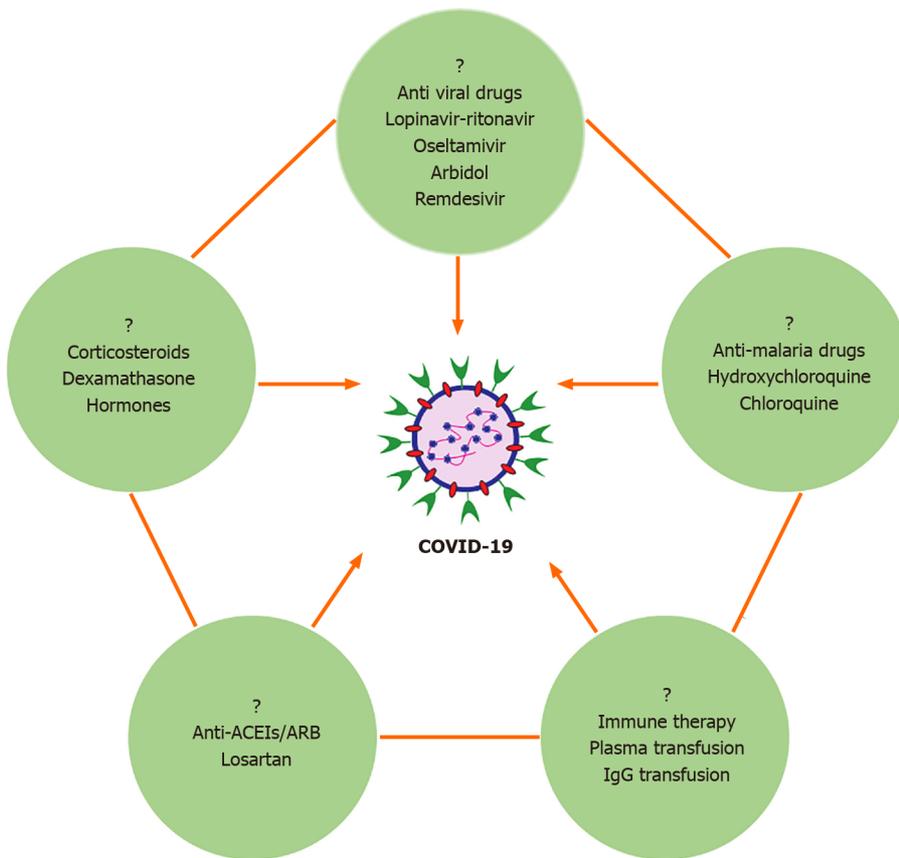
In December 2019, an outbreak of coronavirus disease 2019 (COVID-19) in the city of Wuhan, China, spread across the globe within a short period of time and became the latest public health emergency at the international level[13]. As of June 15, 2020, COVID-19 has been recognized in 213 countries and territories, with a total of 7805148 confirmed positive cases and with a total of 431192 fatalities. Infection control and recovery measures are necessary to prevent the current pandemic situation. It has been observed that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can bring asymptomatic, systemic or respiratory disorders in subjects infected with it. COVID-19 disease is characterized by serious upper respiratory illness including lung failure and pneumonia[14], where the cause of disease was COVID-19 virus [World Health Organization (WHO) named on February 11, 2020] and has been identified as a new novel coronavirus, which is now confirmed as SARS-CoV-2[13,14]. Earlier two major outbreaks of corona viruses occurred, namely Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV, posing a great threat to public health; however, these diseases were not deemed as pandemics. The SARS-CoV-2, which emerged in 2002, is a zoonotic corona virus similar to that of SARS-CoV[14,15]. As COVID-19 has triggered enormous human casualties and serious economic losses globally, an understanding of the ongoing situation and the development of strategies to contain the virus's spread are urgently needed. COVID-19 has caused a disturbed lifestyle, colossal human deaths, and pressing industrial losses globally and within a short period. This outbreak calls for urgent and effective measurements, anti-viral

therapeutics, and the establishment of effective strategies to restrain the virus. Several scientific explorations, particularly meta-studies are providing a great amount of evidence to adapt various therapeutic choices including immune therapy, anti-viral drugs and even the use of traditional medicines to treat COVID-19 infection. Hence, in the current review, we aim to review the status of all meta-studies published from 2019-2020 focusing on therapeutic options for COVID-19 to highlight future directions in the development of safe and successful therapeutic agents to prevent the viral disease (Figure 1).

## THE PATHOGENESIS OF COVID-19

Though the initial transmission of COVID-19 was reported in Wuhan City, China, the actual source, reservoirs or intermediate carriers of the virus are still unknown. The latest COVID-19 viral genome has 88% similarity with SARS-CoV, which are derived from bats. The similarity also suggests that no birds or reptiles can host this virus except mammals[16]. Though the information on primary reservoirs of COVID-19 remain unclear, the transmission from person-to person *via* virus laden released during sneezing, coughing, or direct contact with infected person was reported[17]. Studies also confirmed that there is no transmission of virus from mother to child during pregnancy[18]. The first step of viral infection is the binding of viral spikes with cell-surface receptors of host cells and subsequent fusion with the plasma membrane, specifically on the epithelial cells of the lungs. Studies have investigated and confirmed that COVID-19 shares similarity in the receptor-binding domain of the SARS-CoV and interacts with angiotensin-converting enzyme 2 receptor (ACE2) present on the upper respiratory tract cells to gain invasion into the host system[17]. Moreover, a very recent study identified a group of human's proteins able to interact with SARS-CoV-2 proteins and these host proteins exhibit a range of functions at the cellular level (including DNA replication, vesicle traffic, mitochondrial, nuclear transport, cytoskeleton, lipid modifications, epigenetic regulators and ubiquitin ligases)[19].

It has been observed that SARS-CoV-2 can bring asymptomatic, systemic or respiratory disorders in subjects infected with it[20,21]. An incubation period of 5.8 d was seen in patients infected with COVID-19 with no symptoms and only after this incubation phase, the symptoms of COVID-19 appear from mild to life-threatening illness within 6 to 41 d, with an average of 14 d[20,21]. The appearance of symptoms after the incubation period depends on age as well as the individual's immune system. The common systemic symptoms of COVID-19 infection are fever, dry cough, fatigue, headache, dyspnoea, gastrointestinal symptoms, lymphopenia and haemoptysis[22]. The life-threatening respiratory disorders such as pneumonia, respiratory distress syndrome, acute cardiac injury, serum SARS-CoV-2 viral load (RNAemia), and prevalence grand-glass opacities in lungs were also reported[22]. Patients infected with COVID-19, who experienced breathing difficulties and pneumonia, also had high levels of pro-inflammatory cytokines and chemokines (granule cell stimulating factor, granulocyte-macrophage colony-stimulating factor, interleukin (IL)1- $\beta$ , IL1RA, IL7/8/9/10, fibroblast growth factor 2, interferon  $\gamma$ , IP10, MCP1, MIP1 $\alpha/\beta$ , platelet-derived growth factor B, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and vascular endothelial growth factor A) in the serum; these cytokines and chemokines are related in promoting disease progression[23]. At present, the world is not prepared to face pandemics like COVID-19 and is suffering from its consequences. Until today, there are no functional therapeutic drugs to treat the COVID-19 viral infection. However, COVID-19 patients are receiving supportive care, oxygen supply *via* ventilators and fluid management to overcome symptoms; nonetheless, there are tremendous efforts for vaccine development are undergoing. The global research community and pharma industries are working closely to find a cure for COVID-19 yet remain unsuccessful due to lack of existing evidence about druggable agents, which can provide a safe and sustainable cure for COVID-19 infection. The one possible way to accelerate the discovery process is to look for relatable drug agents that are primarily used in pneumonia, SARS-CoV and MERS-CoV infections. A wide variety of druggable agents or strategies those are known to work against deadly viruses such human immunodeficiency virus and Ebola can also be adapted; however, a clinical validation is needed. To accelerate the discovery of a druggable agent, a clear validation and generalizations of existing information on corona viruses and their killer is useful. To achieve such goals meta-studies are the only source. Hence, in the following sections, we will highlight the evaluations of meta-studies conducted on various possible drug agents



**Figure 1 Coronavirus disease 2019 and its possible treatments.** COVID-19: Coronavirus disease 2019; ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; IgG: Immunoglobulin G.

against COVID-19 to find the most suitable and reliable cure.

**Meta-analysis and COVID-19 therapeutics**

The synthesis of scientific results from pooled data can help us to compare existing results in order to comprehend epidemiology, mortality, management choices, risk assessment and efficiency of prophylactic strategies against COVID-19. When we set the aim to explore the meta-studies on COVID-19 treatment efficiencies, we were unable to find such studies in the databases. The reason could be due to the lack of sufficient or compelling experimental evidences or clinical investigations to perform meta-analysis on prophylactic strategies against COVID-19. However, a few groups tried to find the pattern in aetiology, comorbidities and pathological variations and risk factors of COVID-19 at length[24-27]. Zhong *et al*[28] tried to perform systematic cum meta-analysis on the efficiency and safety of prophylactic strategies against COVID-19. Since the available data on such a topic was less, they tried to evaluate SARS-CoV and MERS-CoV therapies to find relatable and promising treatment options for SARS-CoV-2 infection[28]. In their meta study, antiviral drugs such as lopinavir/ritonavir, ribavirin and anti-malaria drug hydroxychloroquine based clinical data on SARS-CoV, MERS-CoV and COVID-19 was evaluated and found that, altogether, there was an improved mortality rate and reduced clinical development and radiographical improvement but no clear conclusion on the eradication of virus, the incubation phase, the prevalence of acute respiratory disease syndrome and adverse events[28]. However, a subgroup evaluation confirmed that use of ribavirin and corticosteroids in combination had a positive effect on reducing mortality and hydroxychloroquine, which was demonstrated on radiographical outcomes alone. In addition, use of a combination of lopinavir/ritonavir exhibited better eradication of the virus and improved radiographical appearances with a low prevalence of acute respiratory disease syndrome. Keeping the side effects of the drug combination tested into consideration, the quality of verification on most end results were very low and disappointing[28]. Though the meta-analysis failed to draw direct conclusions, due to the heterogeneity and low quality of evidence and indications, the study is still useful for clinicians to thoroughly acknowledge the dos and don'ts of individual anti-

coronavirus agents on efficacy and safety. On the other hand, Etoom *et al*[29] recently commented on one meta study published by Hu *et al*[30] titled “Prevalence and severity of COVID-19: A systematic review and meta-analysis”. The former group thinks a much deeper and careful statistical strategy is needed to evaluate the available evidences on COVID-19. They also suggested that meta-analysis data should be made available, especially in the case of COVID-19, since the number of research explorations are growing immensely and performing new meta-analysis would be easier and quicker[29,30]. We believe, at this stage meta-studies on COVID-19 and therapeutics efficiency might take time because of the lack of sufficient empirical data and since the rate of research investigations are actually yielding low successful outcomes. Nonetheless, we look forward to see an increase in meta-studies aimed at COVID-19 research outcomes. It is noteworthy to mention that, though there were no meta-studies on efficiency of prophylactic strategies against COVID-19, there are a few systematic reviews on the same subject. Meta-analysis and systematic reviews stand atop in estimating the quality of evidence known as “evidence pyramid”. Systematic review does not require statistical analysis, but provides a comprehensive synopsis of scientific literature to a specific research question.

### **Systematic reviews and COVID-19 therapeutics**

In order to curtail the current SARS-CoV-2 global crisis, rapid diagnostics and effective therapeutics are the key potential interventions, which are currently occurring. Moreover, the lessons from previous outbreaks have shown that earlier therapeutics can still be questionable for the use in the current pandemic. Among the ongoing clinical investigations, some of them are testing against SARS-CoV and MERS-CoV while the rest are focused on SARS-CoV-2; however, currently, there is no success of effective therapeutics specific to SARS-CoV-2. The ways to eradicate SARS-CoV-2 include anti-viral drugs, immune therapy, immune boosters, vaccines, anti-malarial drugs, monoclonal antibodies and convalescent plasma, which are majorly monitored by pharma and research investigators. The ultimate goal is to develop anti-corona therapeutics; to accelerate such processes, every effort made is accountable and systematic generalization of such progresses play an important role in deciding the efficacy and safety of individual anti-coronavirus agents. In this hour of need what we want is a magic bullet to stop COVID-19; however, it is not easy to identify, testify, validate and get approval for such magic bullet. Constant efforts from biologists, pharmacists and policy makers are needed to evaluate the efficacy of anti-corona therapies and we are running out of time. We have highlighted the evidence collected through systematic analysis on anti-corona therapies to bring a comprehensive, evidence-based evaluation under one roof to further increase the understanding on the current success rate of anti-corona therapies. An overview of some of the most relevant systematic reviews (SR) and meta-analysis (MA) studies conducted on therapeutic strategies specific to COVID-19 are given in [Table 1](#).

### **Systematic evaluation of anti-viral drugs specific to SARS-CoV-2**

The ongoing antiviral drugs against COVID-19 are mostly similar to MERS-CoV and SARS-CoV-1 studies. A recent study conducted a systematic review on the current clinical settings of antiviral therapies against COVID-19[8]. The study also conducted a similar evaluation on MERS-CoV and SARS-CoV-1 studies to filter potential antiviral drugs. In their analysis, only one clinical investigation involving lopinavir-ritonavir in management of COVID-19 was found, where the treatment had no benefit in 199 severe COVID-19 patients[8]. It is noteworthy to mention that other observational studies, where anti-viral drugs such oseltamivir, lopinavir-ritonavir, lianhuaqingwen capsule, arbidol and interferon were used in the management of COVID-19, could not yield positive conclusions due to the lack of data recording and appropriate sample sizes[8]. Most interestingly, the team could not find any clinical settings where the effects of anti-viral drugs were tested against MERS-CoV and SARS-CoV-1 infections[8]. From the above conclusions, we believe that the current pandemic is more challenging to curb and will be difficult and even more challenging to develop an ideal anti-viral drug to manage severe COVID-19 diseases. Another team also aimed to evaluate the prophylaxis of anti-retroviral drugs on COVID-19 using systematic review to generate strong evidence to support anti-viral drugs as the first line of treatment. They reported the availability of 21 observational studies and two randomized trials, which showed the end results on the use of lopinavir-ritonavir on MERS-CoV, SARS-CoV-1, and COVID-19 patients[31]. From their evaluation, it was suggested that there were no clinical benefits from randomized trials, no inconclusive outcomes from observational studies and a low body of evidence across all major end points, indicating that the use of lopinavir-ritonavir anti-viral drugs as the first line of

**Table 1 Synthetic of evidence on coronavirus disease 2019 specific therapeutic strategies**

Nature of therapeutics	PMID	Study type	Therapeutic	Benefits	Conclusion
Anti-viral drugs	32360583	SR	Lopinavir-ritonavir or ribavirin	Improved mortality rate, radiographical improvement and reduced clinical development	Inconclusive evidences, low quality of evidence and heterogeneity of interventions
	32309809	SR & MA	Lopinavir-ritonavir or Arbidol or Oseltamivir or Lianhuaqingwen capsule or interferon	No benefits in 199 subjects	Side effects. Inconclusive evidence lacks of data recording. Sample size
	32493740				
	32293807	SR	Lopinavir-ritonavir	No clinical benefits	Adverse side effects. Inconclusive outcomes. Low body of evidence. Small sample size
	32506110		Remdesivir	No clinical benefits	Inconclusive outcomes high-quality evidence well-designed studies. Safety
32378648					
Immune therapy	32406927	SR	Plasma transfusion	Had beneficial outcomes	Side effects. Inconclusive outcomes. Very low-certainty. High risk of bias. Low reporting quality
	32272396		Plasma therapy or hyperimmune immunoglobulin transfusion	Had beneficial outcomes	More evidence. Promising strategy. Sample size. Lack of control group
	32527348				
Anti-malaria drugs	32359203	SR	Hydroxychloroquine/Chloroquine	Had beneficial outcomes	Inconclusive outcomes. Methodological flaws. Risk of bias. Lack of evidence
	32281213			No clinical benefits	Lack of evidence. Safety issues
	32468425				
	32173110				
	32519281				
Hormone therapy	32283144	SR & MA	Corticosteroids	No clinical benefits	Lack of evidence. Adverse side effects. Methodological flaws. Caution needed
	32409522	SR			
	32372026				
	32391369				
Anti-hypertension drugs	32542337	SR & MA	ACEI/ARB	Had beneficial outcomes	Conflicting results, scarce existing data. Diverse study types. Inconsistent clinical studies, more RCT needed

ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin-receptor blockers; RCT: Randomised controlled trial; SR: Systematic reviews; MA: Meta-analysis.

treatment is not efficient on COVID-19 patients[31]. The team highlighted that reliability of the proof of end results across MERS-CoV, SARS-CoV-1, and COVID-19 is very low. They also suggested that, in addition to small sample size, the dose, duration and timing of the treatment was not uniform. Moreover, a combination of antiviral drugs along with other interventions may have given rise to the disclosed outcomes[31]. Though both studies differed on trivial aspects of anti-viral drug efficacy against COVID-19, MERS-CoV and SARS-CoV-1 infection, the studies did agree on one common finding, that the use of lopinavir-ritonavir on severe COVID-19 is not efficient. Currently, nearly twenty-five clinical trials are registered and each of the plans are investigating the efficacy and safety of anti-viral agents, including cobicistat, ritonavir, darunavir, lopinavir-ritonavir and tenofovir alafenamide fumarate.

**Systematic evaluation of immune therapy specific to SARS-CoV-2**

The reason behind choosing immune therapy against COVID-19 is because of the

presence of clinical features, such as lymphopenia, increased inflammatory cytokines, chemokines and reduced IFN- $\gamma$  expression in T cells, which indicate suppression of the host immune system against severe COVID-19 infections[32]. The strategies to boost the host immune system through neutralizing antibodies or vaccines are focused on provoking the immune system to fight against COVID-19. However, in the case of COVID-19, the most popular known immune therapy is hyperimmune immunoglobulin transfusion or plasma therapy with nearly 48 studies aimed to evaluate hyperimmune immunoglobulin transfusion or plasma therapy for COVID-19 infected people. A rapid systematic review conducted by Valk *et al*[33] assessed the risks and benefits of using plasma transfusion as a potential immune therapy for COVID-19[33]. They reported that the majority of studies identified adverse side effects (grade 3/4) and that the quality of the reported data was low on plasma transfusion. The data deposited on plasma transfusion studies was highly inconsistent, making it difficult to draw outcomes with certainty[33]. Moreover, some of the controlled non-randomised or randomised controlled investigations are still occurring and have not reported any data regarding the harms and benefits of convalescent plasma therapy[33]. Though the plasma therapy looks promising, the current, global systematic analysis it is not efficient and safe. However, the effectiveness and safety of plasma transfusion remain elusive when compared with other immune therapeutic strategies.

Another study performed a systematic review on probable immune therapies for COVID-19. In this study, the authors included evidences from MERS-CoV, SARS-CoV and SARS-CoV-2 infections, in which the safety and efficacy of immunotherapy was investigated[34]. The highlights of the study primarily come from a single ethnic group (in China); evidence was reported in clinical settings, where the use of plasma therapy (300 subjects), hyperimmune immunoglobulin transfusion (80 subjects), thymosin in combination with camrelizumab (120 subjects) and tocilizumab (188 subjects) against COVID-19 were tested[35]. Though the outcomes of the studies with plasma therapy or hyperimmune immunoglobulin transfusion reported clinical improvements in COVID-19 patients, the evidence to support such therapies fails to provide certainty and demands for further investigations on a large-scale and more diverse population[34]. Moreover, the end outcomes of thymosin/camrelizumab combination therapy and tocilizumab against COVID-19 have yet to be tested. However, the study recommends to test the efficacy and safety of interventions like viral-vectors, vaccines, nanoparticles, and monoclonal antibody against COVID-19 infection, since those have been tested for SARS-CoV in non-clinical settings[34]. Another study performed a systematic analysis to determine the efficacy and safety of immune suppressive/stimulating drugs, such as non-steroidal anti-inflammatory drugs, TNF- $\alpha$  inhibitors, IL-6 inhibitors and Janus kinase/signal transducers and activators of transcription pathway inhibitors. These studies reported that no definite supporting evidence is available from clinical investigations; hence, they recommend clinical investigations using such drugs as promising immune therapeutics, since their efficacy was proved in *in vitro* studies[12]. Whatever approach was adapted by the above-discussed systematics, the end outcome, in terms of using immune therapy for COVID-19, remains dark. The literature is filled with reviews discussing the many possible approaches to prevent COVID-19, but what we need at this moment is more evidence-based studies than narrative opinions.

### **Systematic evaluation of anti-malaria drugs specific to SARS-CoV-2**

In an unusual way, the use of anti-malarial drugs to cure viral infections has become quite popular lately. Malaria is caused by a parasite, *Plasmodium*, and COVID-19 disease is caused by the human corona virus; there are no structural or pathological similarities between the virus and the parasite. However, they both definitely increase body temperature upon infection. The earlier use of anti-malaria drug, such as chloroquine, against human corona viral infections in mouse models was reported in 2009[36]. Due to the public health emergency from SARS-CoV-2, every possible means to prevent viral infections was predicted and being tested. Hence, anti-malaria drugs are currently one of the drugs being evaluated for their efficacy and safety against SARS-CoV-2 in humans. A systematic review conducted found evidence regarding the effectiveness of anti-malaria drugs as anti-viral drugs to prevent SARS-CoV-2[37]. The team reported seven clinical trials, which were evaluating hydroxychloroquine/chloroquine as therapy for SARS-CoV-2, as complete. The end outcomes of the study suggest that both hydroxychloroquine/chloroquine were effective compared to supportive care or anti-viral drug treatment of SARS-CoV-2[37]. However, the outcomes are not reliable, since the evaluated studies has methodological flaws and risk for bias, indicating a lack of evidence to support anti-malaria drugs on SARS-CoV-2. However, hopefully, the data from ongoing trials may provide some evidence in the

future[37]. Another study found similar outcomes upon systematic revision of prophylactic outcomes of hydroxychloroquine and chloroquine against SARS-CoV-2; here, the team concluded that there is a lack of evidence to support hydroxychloroquine and chloroquine routine use and there are potential safety issues, which need to be further evaluated[38]. Another study screened nearly 663 articles and 12 clinical trials, validated the use of hydroxychloroquine and chloroquine against SARS-CoV-2 and found that some of the studies had better clinical outcomes with hydroxychloroquine or combination of azithromycin/hydroxychloroquine use in COVID-19 patients. However, these studies also had major flaws in their methodology. Moreover, a few studies showed adverse and opposite outcomes with hydroxychloroquine[39]. Similarly, another study reported similar observations and came up with a few recommendations, like employing a proper approach based on Monitored Emergency Use of Unregistered Interventions or WHO guidelines in upcoming clinical settings, especially with the use of anti-malaria drugs[40]. We also believe that a better-quality and stringent studies design and inter-relatable data from clinical trials originating across the globe are needed to clear the air regarding the use of hydroxychloroquine and chloroquine against SARS-CoV-2. It is noteworthy to mention that not only systematic reviews but also meta-analyses confirm the ineffective role of hydroxychloroquine in treating COVID-19 patients[9]. The Meta study confirms that there was no effect on viral eradication and a significant mortality rate was seen in COVID-19 patients treated with hydroxychloroquine[9].

### **Systematic evaluation of corticosteroids specific to SARS-CoV-2**

Steroid hormones exhibit an inhibitory role on inflammation, when used in viral pneumonia; hence, many physicians recommended corticosteroid therapy as a possible treatment for patients with COVID-19. Though corticosteroid does not affect the virus directly, this therapy may help in managing severe inflammation and regulate homeostasis. Thousands of people infected with COVID-19 were treated with corticosteroid alone or in combination with anti-viral drugs. Meta-analysis and systematic reviews conducted on finding evidence in support of corticosteroid therapy for SARS-CoV-2 suggested that hormone therapy is ineffective and provokes adverse side effects.

A study by Yang *et al*[41] found that only patients with severe COVID-19 require hormone therapy and routine use of corticosteroid; these patients showed an increased mortality rate, bacterial infection and low blood potassium levels[41]. A caution must be taken while considering corticosteroid as a therapeutic option for mild symptoms[42]. Overall, the study finds inconclusive results, such as sample size, risk of bias in outcomes and the lack of data from multi-centre clinical trials[41]. A different meta-analysis ruled out the safety and efficacy of corticosteroids in SARS-CoV-2 infections. When they tested the virus' clearing effect by corticosteroids, they observed a slow virus clearing rate in two studies[43]. The meta-analysis concludes that there was no improvements in the death rate or the length of stay, which was accompanied by adverse effects[43]. Due to predominance of observational trials in the meta-study, a demand for confirmation from randomized trials to overcome the publication bias is needed[43]. Additional studies also concluded that the current evidence does not fully recommend the use of corticosteroids in SARS-CoV-2 infections; however, a few outcomes recommend the use of methylprednisolone to decrease the mortality rate in severe SARS-CoV-2[44,45].

### **Other notable mentions**

While we discussed the most popular strategies employed in treating COVID-19, it is also important to explore other strategies employed in curing SARS-CoV-2 infection, such as remdesivir, anti-hypertension drugs and Traditional Chinese Medicine. Remdesivir is a broad-spectrum, anti-viral nucleotide analogue that has gained significant attention lately. In preclinical studies, remdesivir has been known to block a range of corona viruses and improve lung function therapeutically; however, the efficacy of remdesivir in COVID-19 patients remains short and scattered. The drug remdesivir received approval to be used under "Emergency Use Authorization" against severe COVID-19 cases, but is still awaiting approval by Food and Drug Administration. A recent systematic review conducted assessed the current evidence on the efficacy and safety of remdesivir and found favorable evidence as a first line treatment option in SARS-CoV-2[46]. The study reported that in order to confirm and recommend remdesivir as high quality and bias free, evidence from clinical settings is needed. Moreover, clinical settings should qualify with larger sample sizes, constrictive design and well-recorded data to synthesize an effective conclusion[46,47]. Furthermore, the future is hopeful with these ongoing trials and these

studies may provide effective evidence on the benefits of remdesivir in COVID-19[47]. The second choice that was opted to treat SARS-CoV-2 infection was inhibitors of the angiotensin receptor or ACE, a possible way to block viral interaction with receptors on lung epithelia cells. Meta studies on Angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers (ACEIs/ARBs) inhibitor-based treatment on SARS-CoV-2 concluded that using inhibitors of ACEIs/ARBs can be continued but large studies such as randomised controlled trial are needed and additional evaluation on the relationship between polymorphism of ACE2 and its inhibitor is a must in the future investigations[48,49]. On the bright side, the upcoming outcomes from clinical trials (NCT04312009 and NCT04311177) using anti-ARB drug (losartan) in COVID-19 hold promising insights. The third choice that was opted to treat SARS-CoV-2 infection was a combination of Western medicine with TCM. One study aimed to investigate the benefits and harms of herbal medicine and Western medicine over COVID-19[50]. The amalgamated therapy rapidly increased the overall effective rate with better clinical outcomes in COVID-19 patients with zero side effects. However, additional evidence from randomized clinical trials may help to validate the benefits or harms of integrated medicine in the treatment of COVID-19[50]. Another study also showed that integrated medicine has beneficial effects when compared to Western medicine alone. The combination therapy did not yield any adverse effects in COVID-19 subjects. The number of studies included quality of data but poor methodologies were adapted in tested studies; a demand for more evidence with good quality to make definite decisions about combination therapy is needed in the future[11]. Effective vaccines are curial in the long-term to prevent rapid transmission of SARS-CoV-2 infections but developing vaccines is time consuming. However, the current crisis is pushing the limits of vaccine development and a few vaccines are being investigated in clinical trials right now. Table 2 provides the details of vaccines developed and their current clinical state specific to SARS-CoV-2. The preceding vaccines belong to DNA, RNA, inactivated viruses, recombinant viral spike proteins, dendritic cells, minigenes and viral vector-based systems. A vaccine developed by Oxford University and AstraZeneca is the most progressive one to enter phase III study settings; this vaccine serves as hope for a promising cure for SARS-CoV-2. Clinical investigations, clinical clearance and approval from the governing body are prerequisites for any drug, vaccines or therapeutic strategies created. Currently, apart from the ones discussed earlier, a wide range of anti-viral drugs, vaccines, cell therapies and anti-bacterial therapeutics are ongoing to determine the safety and efficacy specific to SARS-CoV-2.

### **SARS-CoV-2 specific drug targets under clinical investigation**

Even though the success rate was low and search for suitable, reliable therapeutic drugs against SARS-CoV-2 continues with extensive hard work. In this section we focus on some of the possible upcoming therapeutics which are under early as well late stages of clinical monitoring. A pilot study pursuing the benefits of using amniotic fluid (NCT04319731) or mesenchymal stromal cells from card tissues (NCT04399889, NCT04345601 and NCT04276987) for patients with COVID-19 and use of amniotic fluid was an approved strategies to minimize inflammation, tissues damage in humans. Use of rhDNase1 inhalation to trap neutrophils increased in circulation due to elevated inflammation is under evaluation against SARS-CoV-2 infection (NCT04409925). Anti-IL-6 antibody named Sarilumab has entered clinical evaluation as a potential mediator to interrupt cytokine-linked respiratory injury caused by SARS-CoV-2 infection (NCT04386239). Mouth or nose cleaning and gargling with povidone-iodine solution is currently undergoing clinical examination (NCT04393792), since povidone-iodine killed SARS-CoV-2 virus effectively in *in vitro* studies[51]. A phase III study aimed to rule out dosing with Sildenafil tablets in SARS-CoV-2, since it was approved by WHO for the prevention of pulmonary arterial hypertension (NCT04304313). A Tyrosine kinase inhibitor, Imatinib mesylate blocked inflammatory responses *in vitro*, *in vivo* and in few clinical trials, is under further examination in a phase III trial on SARS-CoV-2 and hoping to observe reduction in disease severity and inflammation (NCT04422678). Baricitinib, anti-Janus kinase inhibitor was approved to treat rheumatoid arthritis earlier and preclinical studies confirm that it can lower or prevent entry of viruses in to epithelia cells and reduce cytokine release, is under phase III clinical monitoring to use on SARS-CoV-2 (NCT04320277). The use of repurposed bacterial mucosal vaccines Bactek-MV130 in the form of spray is undergoing phase III trial to provide benefits for COVID-19 induced mild pneumonia (NCT04363814). Based on preclinical evidences where increased circulatory Vascular Endothelial Growth Factor was seen in COVID-19 subjects, anti-vascular endothelial growth factor drug namely Bevacizumab (FDA approved to treat certain cancers), is being tested in critical or severe patients with COVID-19 pneumonia (NCT04275414).

**Table 2 Vaccines specific to severe acute respiratory syndrome coronavirus 2 under clinical investigation and their development status**

Vaccine name	Vaccine type	Status	Registration ID	Date of registration	Developer
2019-nCoV	Adenovirus vaccine	Phase II	ChiCTR2000031781	10-Apr-20	Academy of Military Medical Sciences
Ad5-nCoV	Adenovirus vaccine	Phase II	NCT04341389	10-Apr-20	CanSino Biologics
AV-COVID-19	Autologous dendritic cells	Phase IB/II	NCT04386252	13-May-20	Aivita Biomedical, Inc
BBIBP-CorV	Inactivated virus	Phase I/II	ChiCTR2000032459	29-Apr-20	Beijing Institute of Biological Products & Sinopharm
BNT162	mRNA vaccine	Phase I/II	NCT04380701	8-May-20	BioNTech and Pfizer
ChAdOx1	Adenovirus vaccine	Phase II/III	NCT04400838	26-May-20	University of Oxford
Covax-19™	SARS-CoV-2 spike protein	Phase I	NCT04428073	11-Jun-20	GeneCure Biotechnologies
COVID-19/aAPC	Antigen presenting cells	Phase I	NCT04299724	9-Mar-20	Shenzhen Geno-Immune Medical Institute
INO-4800	DNA vaccine	Phase I	NCT04336410	7-Apr-20	Inovio Pharmaceuticals
LV-SMENP-DC	Lentiviral vector system	Phase I/II	NCT04276896	19-Feb-20	Shenzhen Geno-Immune Medical Institute
mRNA-1273	mRNA vaccine	Phase II	NCT04405076	28-May-20	ModernaTX, Inc
NVX-CoV2373	Recombinant Spike Protein	Phase I/II	NCT04368988	30-Apr-20	Novavax
PiCoVacc	Inactivated virus + adjuvant	Phase I/II	NCT04352608	20-Apr-20	Sinovac
V- SARS	Heat-inactivated plasma	Phase I/II	NCT04380532	8-May-20	Immunitor LLC
Vero cells	Inactivated virus	Phase I/II	ChiCTR2000031809	11-Apr-20	Wuhan Institute of Biological Products & Sinopharm

LLC: Lewis lung carcinoma; COVID-19: Coronavirus disease 2019; SARS: Severe acute respiratory syndrome.

Ifenprodil, a drug used to inactivate activated neutrophils and T-cells is under phase IIb/III trial to discover the safety and efficacy in the treatment of SARS-CoV-2 infection (NCT04382924). There is no recorded evidence from all the trials motioned above, so we do not know whether anti-inflammatory drugs, rheumatoid arthritis and anti-septic solutions have any benefits in COVID-19 patients. Noteworthy to mention that the above detailed investigations are based on the evidence gathered from preclinical studies and the benefits of using these repurposed medications against COVID-19 need evidence from these study outcomes. Moreover, the safety and efficacy of these drugs on COVID-19 are forthcoming and we hope the outcomes from these studies provide conclusive, bias free evidences. It seems the new players under investigation are mainly to treat SARS-CoV-2 symptoms and have zero effect on viral load, except for povidone-iodine, which was known to eradicate SARS-CoV-2. The world is eagerly dependent on scientific and pharma community for the discovery of magic bullet to treat COVID-19.

### **SARS-CoV-2 therapeutic challenges and anticipations**

In spite of the worldwide distress, no drug or vaccines is available under approval to treat SARS-CoV-2 infection. So far, clinical reports and synthetic evidence show that reusing of existing anti-viral, anti-malaria, immune stimulators and corticosteroids on COVID-19 disease has been unsatisfactory and unsafe. In order to escalate the identification and validation of anti-SARS-CoV-2 medicine, use of computer based high through put data analysis in finding suitable drug targets is recommended. A broad range of anti-viral agents in preclinical and clinical settings must be evaluated for their safety and efficacy against SARS-CoV-2. We believe that use of repurposed medicines for COVID-19 are going to be part of short-term strategy. In spite of the fact that these relatable treatment options have been prioritized to treat SARS-CoV-2 and the outcomes are biased. These uncovering's highlight an immediate call for novel anti-corona medicines specific to SARS-CoV-2 virus. In the current urgency there are several challenges and overcoming those challenges is crucial in developing novel

anti-SARS-CoV-2 medications. One such hurdle is collection of evidence from preclinical experiments, which is expensive and time-dependent. In the absence of preclinical data, computer-based analysis of target profiling allows either to validate or invalidate the use of predicted drug; permits to accelerate invention of novel and beneficial therapeutics against SARS-CoV-2. Though the operating cost is reduced, the safety profile of those computer-generated targets must be validated at least in clinical settings. Another limitation faced by scientist is the availability of suitable study models (cells, mice and primates) to investigate the virus-host interaction and evaluate the potency of anti-SARS-CoV-2 drugs. In addition, BSL3 Laboratories with suitable study models are very few and conducting experiments in such environments is technically difficult. The development of host-based and/or SARS-CoV-2 based clinical inventions must be prioritized since only one or two of drugs will pass through clinical settings. Toxicity, dosage, availability of drug delivery routes and some other limitations make these drugs to pass through the clinical stage. Normally, the development and clinical approval of vaccine needs more than 10 years of time and efforts, however, vaccine development programs against SARS-CoV-2 are breaking the conventional norms and working hard to launch safe and effective SARS-CoV-2 vaccines as early as possible. It can be more challenging to treat COVID-19 diseases, if the virus develops genetic mutations and/or drug resistance during treatment. Studies have reported presence of 93 possible mutations and among them majority of mutations were missense mutations and the genome of SARS-CoV-2 was found to be highly conserved[52]. Also, patients with underlying health issues such as diabetes, cancer, renal failure and women with pregnancy need exceptional care. In addition, management of COVID-19 patients has become challenging due to lack of sufficient medical staff, availability of drugs, subject recognition's, isolation and implication of control procedures and delivery of personalized care towards COVID-19 patients. New Zealand and few Asian countries managed to contain COVID-19 transmission effectively while compared with most of developed countries like United States and Europe. As the epidemic advances, hunger amid poor countries, influence of lock down on mental status of children and adults may increases. To avoid upcoming foreseeable future, systematic and unified approach is vital for managing COVID-19 epidemic. A single drug or a combination approach to preventing COVID-19 disease is needed to prevent mortality, restore the normal lifestyle and economic growth worldwide. The ideal drug must be able to kill virus load with zero or less toxicity in humans, affordable with minimum production time.

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## CONCLUSION

In this real-time crisis, a need for high-quality, bias-free, and effective evidence in eradicating the SARS-CoV-2 virus and reducing disease-associated symptoms with zero side effects is needed. Currently, the journal database is filled with narrative research and speculations with hypothetical reasoning; data on evidence-based research is limited. A shift in evidence originating from original research investigations and clinical studies with high-quality evidence is needed and this evidence may aid in progressing towards the development of effective and safe therapeutic options for SARS-CoV-2. Moreover, the systematic reviews and meta-studies are providing substantial evidence and clearing the air of bias for the public, physicians, and scientists. Drugs like hydroxychloroquine/chloroquine or remdesivir have gained a lot of attention in the public and the media; these drugs have also gained support from experts and are now being characterized as effective therapeutic drugs for SARS-CoV-2 but scientifically it is unwise to recommend these drugs to treat SARS-CoV-2 without caution. Currently, there are no effective anti-viral agents, immune therapy, or vaccines against SARS-CoV-2 but the future is filled with only hope. The current scientific evidence hold inconclusive outcomes because of the low number of studies conducted, low sample size, flawed study designs, publication bias, heterogeneity, missing data records, quality of evidence, ethnicity and presence of adverse effects. However, these flaws cannot stop current and future investigations to identify, characterize and validate possible therapeutic innovations specific to SARS-CoV-2.

### **Future directions**

So far, considering the trajectory of COVID-19 pandemic, the primary need to control the transmission of the disease is to practice physical distancing, wearing masks, keeping hands off from surfaces, and washing them with proper detergent. These rules have somewhat provided the needed protection. The public is well aware of the

facts to restrain themselves from being exposed. Developing surfaces or masks that can kill the virus within seconds once contact made could be a way to prevent highly transmissible virus-laden droplets that are just released. Coming to the scientific role in finding a cure, it is very crucial to understand the genetic profile of the virus at the molecular level and use this knowledge to build safe tools to screen, identify and develop therapeutics for the prevention and treatment of SARS-CoV-2. Currently, no laboratory in the world has whole virus to study in detail. Hence, it is only fitting to build the tools and resources that can be utilized for evaluating therapeutic efficacy. The journey to finding a vaccine or an anti-viral therapy specific to SARS-CoV-2 must start from the basic research integrated with advanced technologies such as artificial intelligence, computational biology, nanotechnology, and genome-wide association studies. The efforts made in the past to find the cure for COVID-19 though failed but provided immense knowledge on what not to practice and open new doors of possibility. Currently, applying a single therapeutic strategy, or even a combination of strategies is not enough to cure diseases including cancers and infectious diseases. In the end, prevention is better than a cure.

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