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REVIEW PROF-0-6010

Potential pharmacological and non-pharmacological interventions for coronavirus disease 2019 (COVID-19): A Narrative Review.

Taha Bin Arif[1], Javeria Saquib[2], Ayman Iqbal[3], Shajeea Arshad Ali[4], Farea Ahmed[5]

1. MBBS Final Year Student Dow Medical College, Dow University of Health Sciences, Karachi.
2. MBBS Fourth Year Student Dow Medical College, Dow University of Health Sciences, Karachi
3. MBBS Fourth Year Student Dow Medical College, Dow University of Health Sciences, Karachi.
4. MBBS Final Year Student Dow Medical College, Dow University of Health Sciences, Karachi.
5. MBBS Fourth Year Student Dow Medical College, Dow University of Health Sciences, Karachi.

Correspondence Address:
Dr. Shajeea Arshad Ali
Dow Medical College,
Dow University of Health Sciences,
Karachi.
shajeeaarshadali@gmail.com

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ABSTRACT… Coronavirus disease 2019 (COVID-19) originated in Wuhan, China, and subsequently spread to 215 countries and territories. Due to the high transmission rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the disease has been declared as a pandemic by the World Health Organization (WHO). Scientists are striving to investigate and contribute new findings of the disease to the literature, especially related to the treatments and preventive measures that can be undertaken to curb its transmission. Multiple studies regarding medical interventions such as antivirals use, mesenchymal stem cell therapy, and convalescent plasma therapy have been published to date. Furthermore, non-pharmacological measures including the usage of personal protective equipment, undertaking proper hand hygiene, and social distancing has been reported to suppress the spread of this infection. However, a definite cure has not been discovered yet. In this review, we have summarized the effectiveness, potential risks, and side effects of all pharmacological agents and non-pharmacological preventive strategies as well as the prospects of possible vaccine for COVID-19.

Keywords: Antiviral Therapy, Coronavirus Disease 2019, Convalescent Plasma, Hand Hygiene, Mesenchymal Stem Cell Therapy, Preventive Measures, Personal Protective Equipment, Severe Acute Respiratory Syndrome Coronavirus 2, Social Distancing, Vaccine.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the seventh member of the family of Beta-coronaviruses that also includes severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and the Middle East respiratory syndrome coronavirus (MERS-CoV).[1] It is an enveloped, single-stranded, positive-sense ribonucleic acid (RNA) virus with an exceptionally high propagation rate and airborne transmission. On December 29, 2019, the first few cases of viral pneumonia in Wuhan were reported to the China Centre for Disease Control, which was later confirmed to be caused by SARS-CoV-2. World Health Organization (WHO) declared it as a pandemic on March 11, 2020, as the disease outbreaks were reported in Asian, European, and American states.[1] According to the WHO Coronavirus Disease 2019 (COVID-19) situation report of July 25, 2020, there have been 15,581,009 documented cases and 635,173 reported deaths globally.[2] It has been estimated that the economic burden of this pandemic would be 1%–2% of Gross Domestic Product (GDP).[3] There is still no specific treatment for COVID-19 because the proliferation and pathogenesis of the virus are unclear. Hence, the medications effective against earlier strains of coronavirus (SARS-CoV and MERS-CoV) are speculated to combat COVID-19. In this article, we have discussed the potential pharmacological and non-pharmacological treatment modalities for COVID-19.

REVIEW

a. Pharmacological Interventions and Research to date

With this ongoing pandemic, significant research studies and trials are being conducted at present in an attempt to find a compelling medicinal cure

for SARS-CoV-2. Lopinavir/ritonavir, remdesivir, favipiravir, ribavirin, interferon, and IL-6 are a few potential drugs under consideration.[4] Usually, there is no need for anti-viral medication since most patients do well without any therapy. Delaying treatment until the patients get severely ill can result in missing an early treatment window when the disease state is somewhat alterable. It is known that anti-viral therapy is most likely to provide benefit when initiated earlier during influenza and severe acute respiratory syndrome (SARS).[5] Therefore, it is logical to begin anti-viral treatment during the early stages of COVID-19, especially in the case of the presence of predictors of adverse outcomes.

Lopinavir Trial for Suppression of SARS-CoV-2, a randomized, controlled, open-label study, investigated the potency and efficacy of oral lopinavir/ritonavir (LPV/RTV) for SARS-CoV-2 infection in 199 hospitalized adult patients.[6] The researchers concluded no adjunct benefit with LPV/RTV beyond standard care.[6] However, it was argued that the disappointing results were a consequence of compromised lung function. Besides, serum levels of anti-virals lower than that required for the inhibition of viral replication in the treated patients questioned their potency.[7] An in vitro study conducted by Wang et al., suggested Remdesivir (RDV), an inhibitor of viral RNA polymerase, as an effective cure to inhibit SARS-CoV-2 in Vero E6 cells.[8] This was further supported by Holshue et al., who reported the recuperation of the first case after being successfully treated using RDV.[9] The fact that the clinical symptoms improved significantly within 24 hours sparked some hope. However, the decrease in viral load of the patient before RDV injection has built-in doubt about the speculation of its relevant use.[10]

A clinical trial conducted in Shenzhen investigated the efficacy of another anti-viral favipiravir, an inhibitor of viral RNA polymerase, in the treatment of COVID-19.[11] Out of the 80 patients selected, 35 received favipiravir, and the rest were controls. The results reported a shorter viral clearance (median 4 days vs. 11 days) and a high rate of improvement in chest imaging (91.43% vs. 62%) in the group that received favipiravir.[11] This research study, along with subsequent trials, confirms the probable use of favipiravir in COVID-19 patients. However, it can be argued that its benefits are subjected to regional differences, as supported by previous studies.[11] It has also been established through diligent researches that interferon-alpha and beta have anti-SARS-CoV-1 activity. Ribavarin, a nucleoside analog, together with LPV/RTV, has been observed to decrease the risk of acute respiratory distress syndrome and deaths than with LPV/RTV alone in SARS-CoV-1.[4] However, it is also worth noting that Ribavarin requires a highly effective concentration to be potent against SARS-CoV-2, as observed in a recent in vitro study.[8]

Gautret et al. proposed macrolide antibiotics, particularly erythromycin, together with hydroxychloroquine as a feasible option for COVID-19 treatment.[12] Patients in the group that received a combination of both medicines were observed to show a decrease in viral load.[12] In contrast, a trial conducted in France reported no such benefit, although they followed the same regimen used by Gautret et al.[13] As far as chloroquine is concerned, its use has widely been accepted by the United States (US) Food and Drug Administration (FDA). This creates an alarming situation since a clinical trial conducted in China found no difference in the rate of viral clearance and clinical outcomes over 7 days in patients with or without hydroxychloroquine.[13,14] A recent report by Ferner et al. highlighted the plausible errors in the results of trials advocating the use of chloroquine.[15] It also drew attention towards the potential adverse effects of chloroquine, such as ventricular arrhythmias, neuropsychiatric disorders, and fulminant hepatic failure.[15]

Caly et al. conducted a clinical trial suggesting ivermectin, an anti-helminthic agent, as a potential drug against SARS-COV-2 inhibiting its replication in cell cultures.[16] This study reported a 5000-fold reduction in viral load after 48 hours of incubation. However, the dose used was 10-fold greater than that approved by the US FDA, and the peak concentration achieved with it was lower than effective in vitro concentrations against SARS-CoV-2.[16] A recent report by Chaccour

et al. claimed that since the ivermectin cross-reacts with Gamma-Aminobutyric Acid (GABA) -gated chloride channels in the mammalian central nervous system, it may cause severe neurotoxicity.[17] However, an analysis of 1,668 reports recorded in the WHO Program for international drug monitoring found only one case of ivermectin-related neurotoxic effects supporting its probable use.[17] Despite this, the US FDA has given out a warning that ivermectin is inappropriate for use in humans.[16] Another anti-parasitic agent, nitazoxanide, has also been considered due to its benefits in the treatment of influenza symptoms using a suggested combination with azithromycin in 8 clinical trials.[18]

The summary of pharmacological agents used to treat COVID-19 is given in Table-I.

Group	Name of the Drug	Mechanism of Action	Adverse Effects
Inhibitors of viral RNA polymerase	Remdesivir	It is an RNA-dependent RNA polymerase inhibitor	No serious adverse effects have been reported until now
	Favipiravir	It inhibits the RNA-dependent RNA polymerase of RNA viruses	Adverse effects such as diarrhea, increase of blood uric acid and transaminases, and a decline in the neutrophils have been observed
Inhibitors of viral protein synthesis	Lopinavir/ ritonavir	Lopinavir is a protease inhibitor. Ritonvair, when combined with lopinavir increases its plasma half-life	Gastrointestinal adverse events such as nausea, vomiting and diarrhea were observed
Viral entry inhibitors	Chloroquine and hydroxychloroquine	They are weak diprotic bases and elevate the endosomal pH, inhibiting viral fusion into the cell. They can also alter the glycosylation of angiotensin converting enzyme-2, the cellular receptor of SARS-CoV-2	They are known to cause ventricular arrythmias, QT prolongation, and can also lead to cardiac toxicity
Immunomodulators	Ivermectin	Ivermectin inhibits the nuclear import of host and viral proteins	It can potentially cause neurotoxicity by cross-targeting the GABA-gated chlorine channels present in the central nervous system

Table-I. Summary of pharmacological interventions which can be used in COVID-19 patients
Abbreviations: RNA, Ribonucleic acid; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; GABA, Gamma-Aminobutyric acid

b. Efficacy of Chinese Herbal Medicine

Chinese Herbal Medicine (decoction, granule, and capsules) was used in around 58.3% of confirmed cases of SARS in 2002.[19] When given concomitantly with Western medicine, it alleviated fever, cough, dyspnea, and other symptoms of pneumonia.[19] Similarly, in four provincial hospitals in China, these herbs were used for symptomatic treatment of COVID-19 with the efficacy of more than 90% and no serious adverse effects. Large scale randomized control trials are yet to be conducted.[20]

c. Ibuprofen for symptomatic relief

The use of Ibuprofen for symptomatic relief of COVID-19 is controversial. In France, the administration of ibuprofen exacerbated the symptoms of disease.[21] These findings were attributed to the fact that the virus adheres to Angiotensin-Converting Enzyme-2 (ACE-2). Ibuprofen can increase the bioavailability of ACE-2; hence the virus proliferates. However, it can be argued that when used in severe infection, the outcome is the result of the disease itself rather than the drug. WHO recommends administrating ibuprofen only when acetaminophen alone fails

to alleviate the fever while strictly weighing the risks against the benefit.[21]

d. Role of Plasma Therapy and antibodies

With the advent of biotechnology, the use of neutralizing antibodies (NAbs) and plasma therapy has played a pivotal role. In the recent years, WHO has recommended treatment with convalescent plasma (CP) taken from patients that had proven to reduce the viral load during outbreaks of different coronaviruses like SARS-CoV-1 (in 2003) and MERS-CoV (in 2012).[22,23]

Chen et al. reported that the treatment of SARS-CoV-1 patients with CP has proven to be effective with no serious adverse effects.[22] However, this claim is contradicting to the statement given by researchers from two medical schools of the United States of America (USA) which state that treatment with CP can pose great risks of deteriorating health conditions such as immune reactions, serum sickness, and infections with other pathogens present in the serum.[23] Moreover, giving plasma infusion to patients with lung infections can put them at risk with transfusion-related acute lung injury (TRALI).[23]

In March 2020, researchers from Shenzen and Tianjin city of China performed a case series in five critically ill patients (age range; 36-65 years).[24] All patients were treated with CP along with anti-viral medications and corticosteroids, which seemed to improve their health conditions. The results were satisfactory as viral loads went down, and partial pressure of oxygen in arterial blood to a fraction of inspired oxygen ratio (PaO2/FiO2) increased within 12 days. It is uncertain if these patients recovered due to treatment with CP alone or whether the other anti-virals played a part in recovery.[24] Moreover, it should be noticed that these patients were exposed to plasma a certain time later in their illness. Hence, it is uncertain about implying that the outcome would be better if they were treated earlier during disease.

Earlier in April 2020, an interesting fact has surfaced that the SARS-CoV-1 and SARS-CoV-2 share structural similarities in the spike protein (S protein).[25] Given that, a recent study showed that NAbs from convalescent SARS-CoV-1 patients could block the S protein-mediated SARS-CoV-2 entry into target cells, which suggests a possible cross-reaction between the two coronaviruses.[25,26] NAbs and immunoglobulins, especially IgG, are immuno-protective and could combat reinfection. However, previous information from SARS-CoV-1 shows that some non-nAbs targeting the non receptor-binding domain (non-RBD) regions in the S protein may elicit an antibody-dependent enhancement (ADE) reaction and cause a harmful immune response. For this reason, SARS-CoV-2 specific NAbs and immunoglobulins are required.[25] Researchers from Pakistan successfully developed and isolated SARS-CoV-2 immune specific IgG antibodies from recovered patients in mid-April 2020.[27] Since early transfusion of immune specific antibodies is an effective treatment for Rabies and Hepatitis B viruses, it is expected that these antibodies may bear a promising result as a breakthrough to combat SARS-CoV-2 infection once the clinical trials begin.

Nevertheless, previous data from the SARS-CoV-1 infection suggests that IgG antibodies pose serious side effects like fever, myalgia, renal failure, and thromboembolism. Certain thromboembolic events were reported in a few patients from Singapore when they were treated with Intravenous Immunoglobulins (IVIG) during the SARS-CoV-1 outbreak.[28] SARS-CoV-2 infected critically ill patients came out to be positive for anti-cardiolipin IgA antibodies and anti–β2-glycoprotein I IgA and IgG antibodies.[29] CP elicits an immune-modulatory response, which helps in neutralizing these antibodies leading to a reduction in thromboembolic events (like antiphospholipid syndrome-like illnesses) and autoimmune conditions.[29] However, to lower the side effects profile of CP therapy, the standard should be met, and the obtained plasma should not be taken from patients with autoimmune conditions and screened for other pathogens. Duan et al. treated 10 COVID-19 patients on mechanical ventilation with 200 mL of CP after taking proper screening measures.[30] All patients showed improvement with a significant reduction in viremia within seven days. The pulmonary

lesions started to regress one to three days post-treatment.[30] A comparison between two studies can be drawn to assess the effects of treatment with CP and Nabs (Table 2).[24,30] Therefore, it is to be kept in mind that IVIG and CP are the two potential therapies that may bear fruitful results for combating SARS-CoV-2 infection.

	Shen C, et al.[24]	Duan K, et al.[30]
Number and characteristics of patients	5 patients (2 females and 3 males with an age range of 36-73 years)	10 patients (4 females and 6 males with an age range of 45-59.5 years)
Co-existing chronic diseases	1 patient had hypertension; mitral insufficiency	4 patients had cardiovascular and/or cerebrovascular diseases and essential hypertension
Treatments	All patients received methylprednisolone and lopinavir/ritonavir or favipiravir or arbidol or interferon alfa-1b	6 patients received i.v. methylprednisolone. 4 patients received arbidol monotherapy, 5 received a combination of arbidol with remdesivir or ribavirin or peramivir, 1 received ribavirin monotherapy
Convalescent Plasma (CP) transfusion	SARS-CoV-2-specific antibody (IgG) binding titer greater than 1:1000	Neutralizing antibody titers above 1:640
Effects of CP transfusion	All patients were receiving mechanical ventilation before CP transfusion out of which 3 were weaned from mechanical ventilation post-transfusion.	3 patients were receiving received mechanical ventilation while 3 were on high-flow nasal cannula oxygenation. Post-transfusion, 2 patients were weaned from mechanical ventilation to high-flow nasal cannula, while 1 patient discontinued high-flow nasal cannula.
	The CT scans of the lungs of all patients showed severe pneumonia prior to CP transfusion. Gradual resolution of pulmonary lesions was observed after the transfusion.	The CT scans of the lungs of a few patients showed massive infiltration and ground glass attenuation. After the CP transfusion, absorption of pulmonary lesions and improved pulmonary function was observed.
	After the treatment, the value of C-reactive protein decreased remarkably while the viral load became negative in all patients.	A remarkable decline in the value of C-reactive protein was observed along with an undetectable SARS-CoV-2 RNA load after CP transfusion.

Table-II. A comparison of 2 studies testing the effects of convalescent plasma therapy on COVID-19 patients
Abbreviations: IV, Intravenous; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; IgG, Immunoglobulin G; CP, Convalescent plasma; CT scan, Computed tomography scan; RNA, Ribonucleic acid

e. Mesenchymal Stem Cell Therapy

Mesenchymal stem cell (MSC) therapy is being considered as a cure of SARS-COV-2 infection as it has proven to reduce the rapid onset of cytokine storm mediated by the immune system and promote endogenous repair by its reparative properties. This is reinforced by a recent case study in China that showed effective cure in

an acute patient of COVID-19.[31] Another study reported a 65-year-old woman with severe SARS-COV-2 infection who was also subject to non-invasive mechanical ventilation.[31] After a cord MSC injection, serum albumin, C-reactive protein (CRP), and alanine aminotransferase (ALT) / aspartate aminotransferase (AST) gradually decreased, white blood cell and neutrophils decreased, and lymphocytes increased to a normal level, as well as other vital signs improved with the resolution of pneumonia. Seven patients affected with SARS-COV-2 at Beijing You' a Hospital underwent MSC transplantation.[31] It resulted in an increase in peripheral lymphocytes, disappearance of activated cytokine secreting immune cells, and a significant decrease in tumor necrosis factor-alpha (TNF-α). Gene expression profiling of MSCs showed that these cells are negative for Angiotensin-Converting Enzyme 2 and TMPRSS2 gene, which codes for transmembrane protease serine 2 enzyme. This demonstrated that MSCs are free of SARS-COV-2 infection.[31]

These trials have substantiated that stem cell therapy can be a potential treatment option for COVID-19. MSCs are easily accessible and can be isolated from various structures such as bone marrow, adipose tissues, umbilical cord, dental pulp, menstrual-blood, buccal fat pad, and fetal liver. They are multipotent stem cells and can quickly expand to clinical volume in a suitable period. So far, the trials have not shown adverse effects associated with allogeneic MSCs.[32]

f. Non-pharmacological preventive measures

As there is no definite pharmacological treatment, certain non-pharmacological measures can help to mitigate the risk and impact of the pandemic, as summarized in Figure-1.

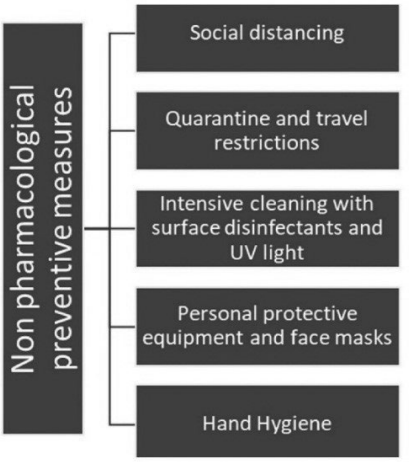

Figure-1. Summary of non-pharmacological preventive measures to curb the transmission of COVID-19
Abbreviations: UV light, Ultraviolet light

Quarantine and Social Distancing to curb transmission

To determine the effectiveness of the quarantine in Wuhan city, a well-mixed Suspected, Exposed latent, Infected and Recovered (SEIR) model was applied to COVID-19 dynamics from January 10, 2020, to February 29, 2020.[33]

The results indicated that reducing the contact rate of latent individuals after quarantine can reduce the number of infected individuals, and hence the peak of infection will be delayed. Unlike SARS and MERS, COVID-19 is readily transmissible even during the incubation period of latent individuals. With no vaccines or definitive treatment available, the only way to curb the transmission will be the strict practice of social distancing, lockdown, and travel restrictions.[33] Wang et al. conducted a study to assess the incidence of COVID-19 among the home quarantined population in Shenzhen.[34] Self-reported questionnaires and nasopharyngeal swab samples were collected from 2,004 participants, out of which only 3 came out to be positive. Hence the results highlighted the significance of a home quarantine with strict avoidance of outdoor events or gatherings in curbing the local transmission. The results can also be attributed to the majority of the participants practicing good hygiene and using face masks.[34] According to a mathematical model, an extended initial lockdown and then a gradual return to activities can reduce the contacts to 40% of the first number before the quarantine implementation.[35]

On the other hand, the ubiquitous practice of social distancing has negative connotations of anxiety, depression, and other mental health problems. It should be rephrased as spatial distancing and social proximity to sustain emotional support

in the communities, especially in low resource countries.[36]

Personal Protective Equipment for Health care workers

While the developed countries are struggling, the situation for low- and middle-income countries is even bleaker. Owing to a limited health budget, the health care facilities face a dearth of ventilators, intensive care hospital beds, and infusion pumps. Being already overburdened with tuberculosis, malaria, and pneumonia, the healthcare systems cannot cope up with the influx of new patients. Overcrowded living conditions and a general shortage of hand sanitizers encourage the local transmission of the disease. Owing to a surge in demand for Personal Protective Equipment (PPE) globally, procuring PPE has become expensive and difficult. This can predispose a lethal risk to health care workers, especially the front liners.[37] Surprisingly, even in the United States, around one-third of health care facilities ran out of masks, with price gougers setting up black markets in New York.[38] Cook TM highlighted that PPE should be used in alignment with the mode of viral transmission; otherwise, limited stocks will be exhausted in the United Kingdom (UK) before the pandemic ends.[39] Droplet precaution PPE [Filtering Facepiece 2 (FFP2), Filtering Facepiece 3 (FFP3), and N95 mask] is suitable for managing a patient within two meters while contact precaution PPE is reserved for a distance of more than two meters.[39] Airborne precaution is only recommended when any aerosol generation is likely such as tracheal intubation, bronchoscopy, cardiopulmonary resuscitation (CPR), high flow nasal oxygen, and mask ventilation.[39] CDC has suggested following a sequence of gowns, masks, goggles, and gloves for putting on PPE and to reverse the order while removing PPE.[40] Houghton et al. highlighted the factors that determine the adherence of healthcare workers to infection prevention and control guidelines.[41] Proper training reinforced by support from the management team facilitated the healthcare workers. Constantly changing guidelines or ambiguous guidelines discouraged them from implementing the protocols.[41]

Testing every patient is difficult and many hospitalized patients may be infected yet remain asymptomatic. Dexter et al. described an evidence-based guideline to revamp the operating room set-up, ensuring perioperative control of COVID-19.[42] As the virus can survive on operating instruments made of stainless steel for at least three days, intensive cleaning with surface disinfectants and ultraviolet (UV) light is recommended.[42] Prophylactic chlorhexidine or nasal iodine povidine should be used to minimize the risk of viral colonization in the patient.[42] Long working shifts for staff can reduce the use and need for PPE. Instead of transferring the patients to a post-anesthesia unit, it is advisable to allow them to recover in the room where they underwent surgery.[42]

Effectiveness of Masks and Hand Hygiene

Masks and Instant Hand Hygiene (MIH) helped in controlling the transmission in countries such as China and Japan. Ma et al. assessed the effectiveness of three different types of MIH, using the avian influenza virus to imitate coronavirus, and a PCR was done to quantify the viral population. N95 masks, medical masks, and homemade masks made of four-layer kitchen paper and one-layer cloth could resist 99.98%, 97.14%, and 95.15% of the virus in aerosols, respectively.[43] Unlike N-95, medical masks were not appropriate for hospital use but could be used in routine interactions. Some randomized control trials negated the efficacy of medical masks in reducing the transmission of viral respiratory infections. However, this study indicated that medical masks can be insufficient but are not completely futile in preventing transmission. It is believed that medical masks elicit a sense of caution and minimize unnecessary hand to mouth or nose contact. Homemade masks are a cheap alternate when medical masks are unavailable. In this study, 1% Soap powder, 0.05%, and 0.25% active chlorine used for instant hand wiping, removed 98.36%, 96.62%, and 99.98% of the virus, respectively. Owing to its surfactant activity, it can inactivate enveloped viruses such as coronavirus.[43]

With the overwhelming number of patients and

the demanding nature of disease management, hand hygiene might be overlooked by the healthcare workers. Behavioral strategies include acknowledging the importance of aseptic working conditions for patient's safety and placing hand rubs to remind the healthcare workers about regular hand sanitizing. Microbiological recontamination can be avoided by adhering to WHO hand hygiene recommendations.[44] It has been reported that incessant and rigorous hand washing without adequate moisturization causes hand dermatitis and skin texture changes.[45] Prolonged water exposure and surfactant activity of soap can alter the ultrastructure of skin and damage keratin. A prior history of eczema and atopic dermatitis makes an individual even more vulnerable. This does not imply discontinuation of handwashing as a wide range of hydrating skin products such as moisture-retaining humectants (propylene glycol), and skin-softening emollients (petroleum jelly) can prevent adverse skin reactions.[45]

g. Prospects of a possible vaccine

So far, no vaccine has been developed. It has been suggested that the therapeutic vaccine for COVID-19 can be created following the same technique used to create a vaccine against infectious bronchitis in poultry with formalin killed Pasteurella Multilocida.[46] The S protein is the primary target for COVID-19 vaccine development as it stimulates the production of virus-neutralizing antibodies. A messenger RNA (mRNA) vaccine is also considered as a promising candidate as it can be upscaled rapidly to meet the increasing global demand. Current status of COVID-19 vaccine development includes four phase I vaccine candidates, six phase II, and two phase III vaccines, as shown in Table-III.[47]

Moderna (USA) initiated phase one clinical trial to test mRNA-1273, a lipid nanoparticle-encapsulated mRNA-based vaccine that encodes for stabilized S protein.[48]

The results for interim phase 1 turned out to be positive as an immune response could be elicited with even a loose dose of 25 μg of the mRNA-1273 vaccine. This has encouraged the team to start a phase 3 study in July.[48] The University of Oxford (UK) is working on a ChAdOx1 vectored vaccine, ChAdOx1 nCoV-19, which is based on an adenovirus vaccine vector.[49] The University of Hong Kong (Pok Fu Lam, Hong Kong) is working on an attenuated variant of the influenza virus that has been modified to express the S protein of the SARS-CoV-2 virus.[49] Even if the vaccine is available, major challenges such as manufacturing, distribution, and accessibility still need to be addressed. It is important to mobilize the pharmaceutical companies for large scale production beforehand so that there is no further delay once a safe vaccine is available.[49]

As multiple countries have participated in the race to create a vaccine; people are expecting its availability soon. Using the classical pathway, vaccine development takes around 10–15 years. Owing to the rare circumstances and persistent efforts of the researchers, human clinical trials will be accelerated and published by the fall of 2020.[50] It is strongly recommended that vaccine developers should test the vaccine in animal models and perform safety trials. Consequently, the urgent demand for a vaccine to curb transmission should not outweigh the safety standards.[51]

CONCLUSION

In the light of literature, as mentioned above, we conclude that pharmacological interventions and non-pharmacological preventive measures play a vital role in controlling the spread of SARS-CoV-2. In the absence of any definite treatment at present, constant trials and case studies by researchers are opening new windows for a probable cure. Treatment using anti-virals with proven efficacy in affected patients together with the practice of quarantine, use of face masks, and maintenance of hand hygiene have cumulatively decreased the spread of the virus. Attempts to establish more sustainable control techniques like administration of MSCs, plasma, and antibody therapy are also looked into with a greater demonstrated success rate. However, there is a strong need for the development of vaccines as earliest as possible to eradicate the pandemic.

Vaccine Candidate	Institution	Stage of Development
Bacillus Calmette-Guerin (BCG) live-attenuated vaccine	University of Melbourne and Murdoch Children's Research Institute, Radboud University Medical Center and Faustman Lab at Massachusetts General Hospital	Phase 3
AZD1222 (Chimpanzee adenovirus vaccine vector)	The University of Oxford and the Jenner Institute	Phase 2/3
mRNA-1273	Kaiser Permanente Washington Health Research Institute	Phase 2
Inactivated vaccine	Henan Provincial Center for Disease Control and Prevention	Phase 2
BNT162	Multiple study sites in Europe	Phase 1/2
BBIBP-CorV (inactivated COVID-19 vaccine candidate)	Henan Provincial Center for Disease Control and Prevention	Phase 1/2
NVX-CoV2373 (prefusion protein nanoparticle vaccine candidate)	Novavax	Phase 1/2
Ad26.COV2-S	Johnson & Johnson	Phase 1/2
Ad5-nCoV (Adenovirus type 5 vector)	Tongji Hospital	Phase 1
INO-4800 (DNA vaccine)	Center for Pharmaceutical Research and the University of Pennsylvania	Phase 1
PiCoVacc (formalin-inactivated and alum-adjuvanted candidate)	Sinovac Research and Development Co., Ltd.	Phase 1
bacTRL-Spike (bifidobacteria monovalent SARS-CoV-2 DNA oral vaccine candidate)	Symvivo Corporation	Phase 1

Table-III. COVID-19 vaccines development

[a]Data obtained from COVID-19 vaccine tracker.[47]

Abbreviations: mRNA, messenger ribonucleic acid; COVID-19, Coronavirus disease 2019; DNA, Deoxyribonucleic acid; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Taha Bin Arif	Reviewed the manuscript and edited it.	Taha
2	Javeria Saquib	Drafted the initial manuscript.	Javeria
3	Ayman Iqbal	Supervised the execution of the entire project.	ayman
4	Shajeea Arshad Ali	Conceptualized the idea and contributed in the initial draft.	shajeea
5	Farea Ahmed	Performed the literature search and gathered relevant data.	Farea