IJISET - International Journal of Innovative Science, Engineering & Technology, Vol. 7 Issue 7, July 2020
ISSN (Online) 2348 – 7968 | Impact Factor (2020) – 6.72
www.ijiset.com

Coronavirus Disease 2019 (COVID-19): A review

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ABSTRACT
Existence of human race has come into trouble due to the coronavirus disease 19 (COVID-19) which is highly contagious viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus initially emerged in Wuhan, China and spread across the globe. Genomic analysis disclosed that SARS-CoV-2 is phylogenetically related to severe acute respiratory syndrome-like (SARS-like) bat viruses, therefore bats could be the possible primary reservoir. Though point of origin and path of transmission is not clearly known, human to human transmission is confirmed through analysis. Due to spread of the disease in about 215 countries around the world, WHO has declared COVID-19 as public health emergency of international concern. There is no clinically approved drug or vaccine available for COVID-19 till date. Scientists are in search of effective and quick cure. Various clinical trials of different antiviral drugs, either alone or in combination with antibiotics, are being conducted worldwide. As the treatment is not available yet, prevention is the only strategy to combat the virus.

KEYWORDS - Coronavirus, COVID-19, Transmission, Viability, Clinical symptoms, Clinical trials, Prevention

HISTORY
Over the course of December of 2019, a cluster of patients with clinical presentations similar to viral pneumonia, albeit of unknown origin was reported in Wuhan, China.[1] Deep sequencing analysis from lower respiratory tract samples of the patients during 24-28 December indicated that the disease was indeed of a viral origin, and the causative organism was found to be a novel coronavirus.[2] While the exact origin of the virus still remains a matter of debate, most of the initial 41-patient cluster had a connection to the Huanan Seafood Wholesale Market, a wet market in Wuhan city that also sold live animals.[3] Another cluster of cases diagnosed as pneumonia of unknown cause was observed on 26 December and treated by Dr. Zhang Jixian, a respiratory medicine specialist in Hubei Provincial Hospital, who then informed the Wuhan Jianghan CDC about the cases.[4] A similar report was also submitted to the hospital authorities and city officials by a group of doctors working in Wuhan Central Hospital following which the Wuhan Municipal Health Commission issued a notice to various medical institutions on "the treatment of pneumonia of unknown cause".[5] However, eight of these doctors, including Dr. Li Wenliang, a Chinese ophthalmologist who later died of the infection, were later admonished by the police for spreading false rumors.[6] From China, the virus quickly spread throughout the world, taking a hold in the European countries of Italy, Spain, Germany and United Kingdom, thus shifting the focus of the outbreak from Asia to Europe. In the recent months, the focus of the epidemic has shifted again to the United States of America, which now leads the world in both number of cases as well as deaths due to COVID-19.[7]

INTRODUCTION

The first official public announcement of a pneumonia outbreak of unknown causes was made by the Wuhan Municipal Health Commission on 31st December, 2019.[8] Over the next month, disease quickly spread throughout the Hubei province and China, as well as crossed international borders. By 30th January, there were 7,818 cases worldwide across 19 countries in five WHO regions. This led the World Health Organization to declare the outbreak of pneumonia caused by the new Coronavirus to be a Public Health Emergency of International Concern.[9]

The causative organism of the disease, which is a new strain of coronavirus was initially named nCOV-2019.[10] Later, the International Committee on Taxonomy of Virus (ICTV) named it Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) because of its genetic relation with the Coronavirus strain responsible for the 2003 SARS outbreak.[11] The World Health Organization, in its statement on February 11, 2020, named the disease caused by the SARS-CoV-2 as COVID-19.[12]

WHY IS COVID-19 DECLARED A PANDEMIC?

An epidemic is defined as the occurrence in a community or a region of a group of illnesses of similar nature, clearly in excess of normal expectancy and derived from a common or a propagated source.[13] A worldwide epidemic is called a pandemic. Like other pandemics before, the COVID-19 epidemic rapidly spread from China throughout the world. By the second week of March 2020, the disease went from a small 41-patient outbreak in Wuhan to a global epidemic infecting more than 100,000 people and killing over 4000 in over 100 countries worldwide.[14] Subsequently, the WHO declared COVID-19 a pandemic on March 11th, 2020.[15]

As of 20th June, 2020, more than 8 million people have been reported to be infected by the SARS-CoV-2 in more than 215 countries and international territories. Of those infected by the disease, more than 4 million have recovered, and over 400,000 people have died of the disease or its complications. The review aims to summarize and discuss information that is currently known about the COVID-19 disease as well as present relevant data on the global scenario of this ongoing pandemic.

CHARACTERISTICS OF SARS-COV-2

COVID-19 is a viral disease, caused by its causative agent, the SARS-CoV-2 virus. It is a member of the family *Coronaviridae* and the order *Nidovirales*. A family of RNA viruses, the *Coronaviridae* family consists of two subfamilies, the *Coronavirinae* and the *Torovirinae*. The subfamily *Coronavirinae* is further subdivided into four genera[16]:

a) Alphacoronavirus containing the human coronavirus HCoV-229E and the HCoV-NL63
b) Betacoronavirus containing HCoV-OC43, Severe Acute Respiratory Syndrome human coronavirus (SARS-HCoV), HCoV-HKU1, and Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV)
c) Gammacoronavirus containing coronaviruses that infect whales and birds
d) Deltacoronaviruses that include virus isolated from pigs and birds.

Coronaviruses are ubiquitous pathogens, and are found infecting large number of vertebrate species, ranging from fishes, amphibians and reptiles to birds and mammals.[17] These are enveloped single stranded RNA viruses,[18] a number of which are human pathogens, causing a variety of diseases including but not limited to respiratory infections, gastroenteritis, hepatitis and encephalitis.[19] Coronaviruses are named as such because of their envelop, which is a spherical lipid bilayer with prominent petal shaped surface projections (spikes) composed of glycosylated type I

glycoprotein.[20] This envelop gives these viruses a 'crown-like' appearance in an electron micrograph, hence the name Coronavirus (in Latin 'corona' means crown).[21] The SARS-CoV-2 is a novel coronavirus belonging to the Betacoronavirus genus[22] along with two highly pathogenic Betacoronavirus strains, the SARS-CoV, responsible for the 2002 – 2004 SARS outbreak[23] and the MERS-CoV, responsible for the 2012 MERS outbreak.[24] Till date there have been 11 complete genome sequences of SARS-CoV-2 isolates from various parts of the world. It has been seen that the genome sequences of different isolates are highly similar between each other (more than 99% sequence identity).[25] Phylogenetic analysis of the SARS-CoV-2 viral RNA indicates that although related, SARS-CoV-2 is genetically distinct from SARS-CoV and MERS-CoV. It is more closely related to bat derived coronaviruses (BatCoV RaTG13, bat-SL-CoVZC45 and bat-SL-CoVZXC21) suggesting a zoonotic origin of the virus, with bats being the original host.[26] However, there is a possibility of there being another yet unidentified intermediate host for the virus. This is due to the fact that while a number of animals (including mammals) were being sold in the Huanan Sea Food market. Furthermore, in Coronaviruses like SARS and MERS, which have bats as the natural reservoir, there were intermediate hosts that helped transmit the virus into humans (palm civets and dromedary camels respectively).[27] Recent research into the identification of intermediate host has implicated pangolins as a probable candidate for the SARS-CoV-2.[28] This uncertainty regarding the origin of the virus and its hosts have led to rampant speculations, with the idea of it being created artificially getting traction in some parts of the populace.[29] However, studies on the genomic analysis of the virus have failed to generate data supporting such a claim.[30, 31]

TRANSMISSION DYNAMICS OF COVID-19

The primary driver of the COVID-19 pandemic is the human to human transmission from symptomatic COVID-19 patients.

(A)Transmission through respiratory droplets:

The primary mode of transmission has been found to be through respiratory droplets, particles more than 5-10 μm in diameter (secreted when the infected person coughs or sneezes)[32] mainly among close contacts of infected patients as evidenced by the presence of clusters of infected family members and healthcare workers.[33] Respiratory droplet transmission occurs when an individual comes in close contact (within 1 meter) with patient who has respiratory symptoms like coughing or sneezing and gets exposed to the droplets. This person is thus at risk of having his/her mucosae (mouth and nose) or conjunctiva (eyes) exposed to potentially infective respiratory droplets.[34]

(B) Airborne transmission:

Although it has been suggested that SARS-CoV-2 might have an airborne mode of transmission.[35] Airborne transmission, also called aerosol transmission differs from droplet transmission in the sense that it occurs through infective viral particle borne within droplet nuclei, particles less than 5μm in diameter which can remain in the air for long periods of time and be transmitted over distances more than 1 meter (infective radius of droplet transmission) through air currents. However, in case of COVID-19, airborne transmission of the virus might be possible in certain situations. Most of these are in the medical setup, associated with activities or procedures or support treatments that generate aerosols during the process; i.e., endotracheal intubation, disconnecting the patient from the ventilator, bronchoscopy, open suctioning, turning the patient to the prone position, administration of nebulized

treatment, manual ventilation before intubation, non-invasive positive-pressure ventilation, cardiopulmonary resuscitation and tracheostomy.[36]

(C) Transmission through fomites:

Transmission may also occur through fomites in the surrounding environment around the infected person, as the virus has been found to persist on surfaces up to 96 hours.[37] Therefore, COVID-19 virus can be transmitted via direct contact with infected person and indirect contact with surfaces in the immediate surrounding or objects used by infected person like towels, cups, clothes etc. or medical instruments used on the infected person, for example stethoscopes, thermometers etc.

The duration for which virus can remain active or sustain in environment is known as viability of virus. All viruses have different viable period from few hours to few days and viability varies from surface to surface as well. Viability of coronavirus (SARS-CoV-2) on common surfaces is given in table-

Table 1: Shows viability of coronavirus on common surfaces[38]

S.No	Surface	Time duration
1	Aluminium	2-8 hours
2	Copper	4 hours
3	Cardboard	1 day
4	Wood	4 days
5	Plastic	2-5 days
6	Glass	4-5 days
7	Ceramic	5 days
8	Paper	3 hours to 5 days
9	Steel	2-28 days

(D) Feco-oral transmission:

SARS-CoV-2 viral RNA has also been isolated from stool samples and toilet bowls of patients suffering from COVID-19.[39, 40] However, whether feco-oral route of transmission is possible for SARS-CoV-2 is yet unknown.

(E) Other modes of transmission:

In a study conducted in an intensive care unit and general wards caring for COVID-19 patients in Wuhan, Zhen-Dong Guo et.al reported that SARS-CoV-2 RNA particles could be isolated from a wide range of places. In this study swab samples were collected from the floors, trash cans, computer mouse, patients' masks, sickbed handrails, air outlets, and personal protective equipment. The authors found viral particles in the floor swabs taken from the two wards as well as from the pharmacy, where there were no patients. Therefore, it was suggested that the virus was carried by shoe soles of the medical staff who walked around the SARS-CoV-2 patient's wards and also went to the pharmacy, depositing viral particles there. However, the authors also mentioned that since their study detected viral RNA, it was not indicative of viable viruses and therefore did not signify transmission.[41]

Modes of transmission :

An April 2 report by the World Health Organization discussed the available evidence regarding symptomatic, pre-symptomatic and asymptomatic human to human transmission of the SARS-CoV-2 virus.

(A) Symptomatic transmission:

In the document, WHO states that most of the cases of human to human transmission of the virus have taken place from people who are infected and showing the symptoms of COVID-19, i.e. symptomatic transmission of the disease.[42, 33]

(B) Pre-symptomatic transmission:

Only a small cluster of patients have been reported who were infected by patients who have been infected by the virus but were in the incubation period of the disease, i.e. in the pre-symptomatic period. These reports were made through contact tracing of the cases and investigations into the clusters of confirmed cases.[43, 44]

(C) Asymptomatic transmission:

There were few reports of asymptomatic transmission of COVID-19 (people getting infected from patients who were infected did not develop any symptoms throughout their infection). However, most of these 'asymptomatic transmissions' were later found to be evidence of 'pre-symptomatic transmission', and the patients were either mildly symptomatic during transmission or developed symptoms later on.[45, 46] However, asymptomatic transmission of COVID-19 still remains a very real possibility that might explain the rapid spread of the disease and therefore cannot be ruled out.[47]

(D) Human to Animal Transmission

On April 6, 2020, a tiger in Bronx Zoo of USA was reported to be infected with the SARS-CoV-2. The animal probably got infected by a pre-symptomatic zookeeper attending it. It was the first reported human-to-animal transmission of the virus.[48] Such human to animal transmission might pose a significant problem in stamping out the virus, as infected animals might act as reservoirs and even intermediate hosts for SARS-CoV-2.

INCUBATION PERIOD

Li et al. reported that the mean incubation period of COVID-19 was found to be 5.2 days in the study analyzing 425 cases.[49] Studies by Huang et al. and Chu et al. have reported median incubation period to be around 3 days and as long as 19 to 24 days respectively.[3, 50] This is comparable to the incubation periods of both SARS (2 – 7 days)[51] and MERS (2 – 14 days),[52] but is longer than that of seasonal influenza (1 – 4 days),[53] suggesting a longer pre-symptomatic phase. R_0 refers to the average number of people that one infected individual can infect in a fully susceptible population.[54] Chu et al. estimated the R_0 to be 2.2, later analyses by Liu et al. reported that the R_0 was 3.28.[55] This is higher than both SARS (2.7)[56] and 2009 pandemic H1N1 influenza (2.4),[57] indicating that the SARS-CoV-2 is more infectious than these two viruses.

PATHOPHYSIOLOGY AND MECHANISM OF ACTION

Betacoronavirus strains, like other members of the *Coronaviridae* family generally show high species specificity. However, being an RNA virus, they are prone to mutations, and these changes in their genetic materials often change not only their pathogenicity but also their host ranges. For example, even though the original hosts of SARS-CoV and MERS-CoV are bats, genetic mutations enabled them to infect humans as terminal hosts, with palm civets and dromedary camels being the intermediate hosts respectively.[58, 59] Since the evidence obtained till now points to similar zoonotic origin of the COVID-19 disease, careful monitoring of the pandemic is required to track the future course of the disease as well as obtain data regarding further mutations in the viral genome that may yet again change its host range, infectivity, and virulence. Recent studies have indicated that SARS-CoV spike protein receptor-binding domain (RBD) binds with the angiotensin converting enzyme 2

(ACE2) receptors of the host cells so as to give the access of the cell to the viral particles.[60] This property of the virus enables it to infect the epithelium of the respiratory system as well as the alveolar pneumocytes type 2 (AT2).[61] The virus then causes lysis of the infected cells, which sets into motion the inflammatory immune response of the host by triggering the release of proinflammatory cytokines like interleukin IL1, IL2, IL 7, interferon gamma, macrophage inflammatory proteins, tumor necrosis factor alpha etc. Excessive immune response by the host coupled with the continued lysis of the infected cells generate a cytokine storm. In presence of cellular destruction, as more inflammatory cytokines are released, more WBCs are recruited which in turn release even more inflammatory cytokines. This leads to extensive tissue damage. causing rapid progression of mild respiratory symptoms like dry cough and fever into Acute Respiratory Distress Syndrome (ARDS) followed by multiple organ failure in susceptible patients.

CLINICAL FEATURES AND DIAGNOSIS

COVID-19 most commonly presents with respiratory symptoms. Fever, fatigue, myalgia, dry cough and dyspnea are commonest symptoms of the disease.[62, 63] However, headache, dizziness, diarrhea, nausea and vomiting have also been reported.[3] People with co-morbidities like hypertension, diabetes, cardiovascular, and cerebrovascular diseases have a higher risk of developing severe forms of the disease, which is associated with pharyngeal pain, severe dyspnea, anorexia and abdominal pain[63] and hemoptysis.[64] Symptoms of acute respiratory infection appear early in the disease, and in people with severe disease progress to septic shock, coagulation dysfunction, ARDS and even death.

Table 2: Symptom profile of COVID-19 in Chinese patients

Study	Huang et al.	Chen et al.	Chung et al.[65]
Fever	98%	83%	67%
Shortness of Breath	55%	31%	-
Cough	76%	81%	43%
Hemoptysis	5%	-	-
Myalgia	44%	11%	3%
Confusion	-	9%	-
Sore throat	-	5%	-
Diarrhea	1%	2%	-

To aid the diagnosis and management of COVID-19, the World Health organization has developed certain case definitions for the disease, although these definitions vary between individual countries. They are:

1. *Suspect case*: A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; **OR** A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset; **OR** A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) **AND** in the absence of an alternative diagnosis that fully explains the clinical presentation.
2. *Probable case*: A suspect case for whom testing for the COVID-19 virus is inconclusive. **OR** A suspect case for whom testing could not be performed for any reason

3. *Confirmed case*: A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms. [66]

For patients fitting the criteria for suspect and probable case of COVID-19, oropharyngeal and nasopharyngeal swabs are sent for laboratory confirmation of the disease through Real Time Polymerase Chain Reaction test (RT-PCR). The most common laboratory diagnostic findings for the Viral genome along with RT-PCR detection are lymphopenia and thrombocytopenia in peripheral blood smear, prolonged activated thromboplastin time and elevated lactate dehydrogenase levels.[67] There have been reports of abnormal serum ferritin and elevated liver enzymes in some patients.[68]

Radiological diagnostic methods have played a critical role in diagnosis of not only early but also in serious cases and management of COVID-19 . X-Ray diffraction in early detection and Computed Tomography (CT) scan of chest of people suffering from pneumonia show multifocal patchy ground glass opacities near the periphery of the lung field.[33] Disease progression is associated with the increasing size and density of the lung opacities. In patients with severe forms of the disease, bilateral multiple lobular opacities with subsegmental consolidations have been reported and may also present with intralobular septal thickening and pleural effusion.[3]

SUSCEPTIBLE POPULATION

Adult population: The population at highest risk of suffering from severe forms of COVID-19 is adult ≥60 years of age and those with comorbidities. Severe forms of the disease may also be associated with coinfections and superinfections by bacteria and fungi.[63]

A study by Jin et al. found that while males and females have same risk of contracting the infection, male patients were more likely to develop severe disease. Women are less likely to not only develop severe forms of the disease but also develop severe complications as compared to men.[69] A study by Chen et al. analyzing COVID-19 infections in pregnant women reported no significantly worse clinical symptom profile in pregnant women as compared to non-pregnant women.[70]

Paediatric population: It has been seen that COVID-19 is seen most commonly in adults than in children less than 15 years.,[62, 71]In pediatric population, COVID-19 presents mostly as mild to moderately severe infections, with severe infections requiring intensive care being quite rare.[72] Children have also been found to have better prognosis than their adult counterparts.[73]

TREATMENT

As SARS-CoV-2 is a new virus, doctors are treating patients on the basis of their knowledge and existing experience. Glenmark Pharmaceuticals got approval from the Indian regulators for manufacturing and marketing of oral anti-viral drug Favipiravir under the brand name of Fabi-flu for the treatment of mild to moderate COVID-19 patients in India[74]. Cipla launches Cipremi (Remdesivir lyophilized powder for injection) is the only USFDA approved Emergency Use Authorisation (EAU) for the treatment of severe COVID-19 patients.[75] Isolation of symptomatic patients is the integral part of the treatment. Patients with mild infections generally need supportive therapy comprised of antipyretics like acetaminophen, external cooling, nutritional therapy inclusive of vitamin C and anti-bacterial therapy for secondary bacterial infections. Various classes of the drugs like antimalarials, antivirals, monoclonal antibodies, anthelmintics are tried in treating COVID-19 infection. Patients with severe diseases, however, require high flow oxygen therapy and extracorporeal membrane oxygenation (ECMO).[76] However, routine administration of systemic corticosteroids in the management of ARDS in critically ill COVID-19 patients is not

recommended. Empiric administration of antibiotic in cases of sepsis with organ function support might provide some benefit in management. Aerosol administration of alpha-interferon and intravenous administration of immunoglobulin have also been seen to provide some benefits.

CLINICAL TRIALS

Hydroxychloroqine & Azithromycin: Of the more popular drugs under consideration, Hydroxychloroquine, an anti-malarial has been suggested to be effective drug to manage COVID-19, both as a prophylactic as well as a therapeutic agent. An open-label non-randomized clinical trial found that hydroxychloroquine when used with Azithromycin, a macrolide antibiotic, was significantly associated with the reduction of viral load in COVID-19 affected patients.[77] This assessment was supported by several other studies,[78, 79] prompting different international agencies and health bodies to start clinical trials of the drug as well as start recommending them as prophylaxis or treatment of the disease. One of these is a randomized double-blind placebo-controlled trial of hydroxychloroquine and azithromycin started by the National Institute of Health and conducted on patients in the United States of America. [80] and the Solidarity trial, a multinational clinical trial of hydroxychloroquine along with three other drug regimens conducted by the World Health Organization.[81] But recent research on this have suggested that use of hydroxychloroquine as a therapeutic agent might have no effect on the improvement of survival of COVID patients,[82] and might even be associated with increased mortality due to its various side effects, most prominently its effect on QTc prolongation in susceptible patients that might lead to fatal arrythmias.[83] A large scale, cross-continental observational study of 96,032 patients further reported that use of Hydroxychloroquine and Azithromycin in the treatment of COVID-19 was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias.[84] Based on these findings, WHO suspended the hydroxychloroquine arm of the Solidarity trial on May 22, 2020. However, further studies have emerged which suggest benefit of the drug regimen as a prophylaxis for healthcare workers[85], and the debate is still ongoing regarding the effectiveness of the drug on the disease.

Remdesivir: Another notable drug that is being studied as a potential treatment of COVID-19 is the broad spectrum anti-viral medication remdesivir. Initial open-label non-randomized clinical trials on a small sample of patients showed reduction of both the mortality and severity (hospital stay) of COVID-19 patients treated with intravenous remdesivir.[86] Although a randomized, placebo-controlled, multicenter trial on the effectiveness of Remdesivir on COVID-19 done in China found no significant benefits of the drug, it did show a reduction in time to clinical improvement in COVID-19 patients.[87] The preliminary report of a large randomized, placebo-controlled, double-blind trial of remdesivir funded by the National Institute of Allergy and Infectious Diseases (NIAID) also showed that Remdesivir was superior to placebo in shortening the time to recovery in adult patients hospitalized due to COVID-19 infection.[88]

Other antivirals experimented for treatment of COVID-19 are Remedesivir, Umifenovir, Hydroxychloroqine, Azithromycin**,** Favipiravir, Ritonavir, Sarilumab, etc.

Multiple ongoing clinical trials to test the effectiveness of different drugs as potential therapeutic agents for COVID-19 are elaborated in Table 3.

Table 3: Ongoing clinical trials for the management of COVID-19[89]

Drug	Company/ Sponsor Investigator	Trial Phase	Location	Start Date	End Date	Tracking ID
Remedesivir	Assistance Publique - Hôpitaux de Paris	N/A	Hôpital Cochin, Paris, France	May 5, 2020	June, 2020	NCT04365725
	Gilead Sciences	Phase 3	St Joseph Hospital Eureka, Fortuna,California, United States	March 6, 2020	May 2020	NCT04292899
	Gilead Sciences	Phase 3	Eden Medical Center, Castro Valley, California, United States	March 15, 2020	May 2020	NCT04292730
	Capital Medical University	Phase 3	China, Beijing	February 6, 2020	April 10, 2020	NCT04257656
	Gilead Sciences	N/A	St. Jude Medical Center, Fullerton, California, United States	-	-	NCT04323761
	National Institute of Allergy and Infectious Diseases (NIAID)	Phase 3	Naval Medical Center San Diego - Infectious Disease Clinic, San Diego, California, United States,	February 21, 2020	April 1, 2023	NCT04280705
Remedesivir, Lopinavir/ ritonavir and Hydroxychloroquine	Sunnybrook Health Sciences Centre **Collaborators:** AbbVie Apotex Inc.	Phase 2	University of Alberta Hopsital, Alberty, Canada	March 18, 2020	May 18, 2022	NCT04330690
Umifenovir	Beijing YouAn Hospital	Phase 4	Huangshi Central Hospital	February 23, 2020	February 28, 2021	NCT04286503
	Jieming QU	Phase 4	N/A	February 7, 2020	December 30, 2020	NCT04260594
	Second Affiliated Hospital of Wenzhou Medical University **Collaborators:** WanBangDe Pharmaceutical Group Co.,Ltd.	N/A	The Second AffIliated Hospital of Wenzhou Medical University. Wenzhou, Zhejiang, China	February 16, 2020	June 1, 2020	NCT04273763
	Jiangsu Famous Medical Technology Co., Ltd.	N/A	Huai'an fourth people's Hospital. Huaian, Jiangsu, China	March 2, 2020	May 2020	NCT04306497
	First Affiliated Hospital of Zhejiang University **Collaborator:**	N/A	N/A	February 7, 2020	June 30, 2020	NCT04261907

	Ascletis Pharmaceuticals Co., Ltd.					
Favipiravir	Fujifilm Pharmaceuticals U.S.A., Inc.	Phase 2	Brigham and Women's Hospital Boston, Massachusetts, United States	April 17, 2020	December 2020	NCT04358549
	Ain Shams University	Phase 3	Faculty of Medicine Ain Shams University Research Institute-Clinical Research Center Cairo, Non-US, Egypt.	April 20, 2020	December 1, 2020	NCT04349241
	King Abdullah International Medical Research Center	N/A	King Abdulaziz Medical City, National Guard Health Affairs Riyadh, Saudi Arabia	May 2020	November 2021	NCT04392973
	Peking University First Hospital	N/A	Ezhou Central Hospital Wuhan, Hubei, China	March 8, 2020	May 2020	NCT04310228
	Baqiyatallah Medical Sciences University	N/A	Mohammad Sadegh Bagheri Baghdasht Tehran, Iran, Islamic Republic of, 0	March 29, 2020	May 25, 2020	NCT04376814
	Peking University First Hospital	N/A	he Second People's Hospital of Fuyang Fuyang, Anhui, China	April 1, 2020	September 15, 2020	NCT04333589
Ritonavir	Huoshenshan Hospital **Collaborator:** Ascletis Pharmaceuticals Co., Ltd.	Phase 4	Huoshenshan Hostipal Wuhan, Hubei, China	March 18, 2020	May 31, 2020	NCT04345276
	The Ninth Hospital of Nanchang **Collaborator:** Ascletis Pharmaceuticals Co., Ltd.	Phase 4	The Ninth Hospital of Nanchang Nanchang, Jiangxi, China	February 17, 2020	March 19, 2020	NCT04291729

	Hospital Universitario de Fuenlabrada **Collaborator:** Centro Nacional de Investigaciones Oncologicas CARLOS III	Phase 2	Hospital Universitario de Fuenlabrada Fuenlabrada, Madrid, Spain	April 13, 2020	September 2020	NCT04346147
	Vanderbilt University Medical Center **Collaborator:** AbbVie	Phase 2	University of Colorado School of Medicine Aurora, Colorado, United States	May 31, 2020	May 1, 2021	NCT04372628
	Shahid Beheshti University of Medical Sciences	Phase 4	Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences and Health Services Tehran, Iran, Islamic Republic of	April 15, 2020	April 24, 2020	NCT04350684
	National Cancer Institute, Naples	Phase 2	Azienda Ospedaliero-Universitaria di Modena Modena, Italy	March 19, 2020	December 19, 2022	NCT04317092
	University of Malaya	Phase 3	University Malaya Medical Centre Kuala Lumpur, Malaysia	April 15, 2020	October 31, 2020	NCT04345445
	University of Chicago	Phase 2	University of Chicago Medicine Chicago, Illinois, United States	April 4, 2020	December 2020	NCT04331795
	Fundació Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau **Collaborator:** Instituto de Salud Carlos III	Phase 2	Hospital de la Santa Creu i Sant Pau Barcelona, Spain	April 2, 2020	October 2020	NCT04332094
	Azienda Unità Sanitaria Locale Reggio Emilia	Phase 2	Ospedale di Guastalla Guastalla, RE, Italy	March 31, 2020	May 30, 2020	NCT04346355

	Genentech, Inc.	Phase 3	N/A	May 8, 2020	October 5, 2020	NCT04372186
	Hoffmann-La Roche	Phase 3	University of California San Diego La Jolla, California, United States	April 3, 2020	September 30, 2020	NCT04320615
Sarilumab	Regeneron Pharmaceuticals **Collaborator:** Sanofi	Phase 2	Regeneron Study Site Los Angeles, California, United States	March 18, 2020	April 1, 2021	NCT04315298
	ASST Fatebenefratelli Sacco	Early Phase 1	N/A	May 2020	December 2020	NCT04386239
	Maria del Rosario Garcia de Vicuña Pinedo **Collaborator:** Instituto de Investigación Sanitaria Hospital Universitario de la Princesa	Phase 2	Hospital Universitario de la Princesa Madrid, Spain	April 13, 2020	June 2020	NCT04357808
Ivermectin	Laboratorio Elea Phoenix S.A **Collaborators:** Universidad Nacional de Salta Centro de Investigación Veterinaria Tandil CIVETAN Hospital de Pediatría Prof Dr. Juan P. Garrahan Universidad Nacional de Quilmes	Phase 2	Centro de Educación Médica e Investigaciones Clínicas "Norberto Quirno" CEMIC Buenos Aires, Ciudad De Buenos Aires, Argentina	May 11, 2020	June 30, 2020	NCT04381884
	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	Phase 2	Johns Hopkins Hospital Baltimore, Maryland, United States	June 2020	June 2021	NCT04374279
Chloroquine	Oxford University Clinical Research Unit, Vietnam **Collaborators:** Ministry of Health, Vietnam	Phase 2	Can Gio COVID Hospital Ho Chi Minh City, Vietnam	April 7, 202	April 1, 2022	NCT04328493

	HaEmek Medical Center, Israel **Collaborators:** T MAY BIOPHARMA LTD.	Phase 2	N/A	April 2020	December 2021	NCT04333628
	UMC Utrecht **Collaborators:** ZonMw: The Netherlands Organisation for Health Research and Development	Phase 4	UMCU Utrecht, Netherlands	April 14, 2020	May 14, 2021	NCT04362332
	Tanta University	Phase 2	Tanta University Tanta, Egypt	April 17, 2020	December 1, 2030	NCT04353336
	Wroclaw Medical University	Phase 4	Uniwersytecki Szpital Kliniczny Wrocław, Ul. Borowska 213, Poland	April 16, 2020	December 31, 2020	NCT04331600
Hydroxychloroquine	Prof. Dr. Umar Farooq **Collaborator:** Ayub Medical College, Abbottabad	Phase 3	Ayub Teaching Institution Abbottābād, K.p.k, Pakistan	March 28, 2020	June 28, 2020	NCT04328272
	General and Teaching Hospital Celje	Phase 4	SB Celje Celje, Slovenia	April 10, 2020	July 31, 2020	NCT04355026
	University Hospital Tuebingen **Collaborators:** Robert Bosch Medical Center Universitätsklinikum Hamburg-Eppendorf Bernhard Nocht Institute for Tropical Medicine	Phase 3	Institute for Tropical Medicine Tübingen, Germany	April 22, 2020	September 30, 2022	NCT04340544
	Hospital St. Joseph, Marseille, France	Phase 3	Hopital Saint Joseph Marseille, Paca, France	April 2020	January 2021	NCT04365231
	Intermountain Health Care, Inc. **Collaborators:** University of Utah	Phase 2	Intermountain Medical Center Murray, Utah, United States	March 30, 2020	December 31, 2021	NCT04329832
	University of Chicago	Phase 1	University of Chicago Chicago, Illinois, United States	April 2020	June 2020	NCT04351620

CONTROL AND PREVENTION STRATEGIES:

Since currently there are no treatment regimens for COVID-19, prevention of the spread of the SARS-CoV-2 virus by breaking the chain of transmission remains the mainstay of management of the pandemic.[90]

Individual settings - Preventive measures aimed at reducing exposure to respiratory droplets, physical contact with patients and fomites used by them, is the key to breaking the chain of transmission. The mainstay of this are social distancing, proper hand hygiene, cough etiquette and wearing of masks and other protective equipment. Social distancing should be followed by each and every person of the general populace by maintaining at least 1 metre (3 feet) distance between oneself and others to avoid the transmission through droplets. Hand hygiene must be ensured by thorough hand washing for at least 30 seconds following all the steps of hand washing. Although the preferred agent for hand hygiene is soap and water, alcohol-based hand rubs containing 60-80 percent ethanol can be used. Masks, preferably NIOSH-certified N95 particulate respirators should be worn whenever a person goes outside/interacts with a suspected case. However, in absence of N95 respirators, disposable three-layered medical masks or even cloth masks have been shown to significantly reduce the chances of transmission of the SARS-CoV-2.[91]

Community setting - In the community setting, symptomatic patients should be isolated, and their contacts traced and tested. People coming from COVID-19 hotspots or in contact with a symptomatic patient in the last 14 days should undergo self-quarantine at home or local quarantine center for a period of no less than 14 days. People in home or in institutional quarantine/isolation should be kept in a well-ventilated, preferably individual rooms so as to minimize transmission from one person to another.

Healthcare setting - Since healthcare setups have the potential to be important sources of transmission of the virus, it is extremely important to follow proper infection control measures in the hospital setup. Suspected and symptomatic cases presenting to the healthcare facility must wear face masks and maintain strict social distancing to prevent the transmission of the disease to other, potentially susceptible people. There should also be a separate, well-ventilated room for them. Medical professionals and other healthcare workers caring for suspected and confirmed cases of COVID-19 must wear full personal protective equipment to prevent transmission of the disease and protect themselves, and by extension, other patients from the virus. Patients requiring hospitalization must be kept in rooms with negative air pressure, filtered through high efficiency particulate air purifier machines (HEPA) with at least six air changes per hour. Once the patients are recovered and discharged, the room must be disinfected thoroughly.[92]

CONCLUSIONS

The COVID-19 pandemic is an international public health disaster that needs prompt and scientifically driven management. At present there is no effective drug/vaccine is available for the treatment, making the disease wild. Rapid development of effective drugs and vaccines is the need of hour. However, owing to the high infectivity of the virus, until a proven treatment/vaccine regimen is established, individual countries should focus on managing the pandemic by focusing on breaking the chain of transmission. Strict adherence to hand hygiene, social distancing, and personal protective measures by the public will play a major role in controlling the disease. Increasing and improving testing-tracing-isolation infrastructure by the governments can go a long way towards defeating SARS-CoV-2 virus.

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