



## STRATEGIES FOR PREVENTION OF COVID-19 IN HEALTH CARE SETTINGS- A SYSTEMATIC REVIEW

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### ABSTRACT

Here, we review the effect of COVID-19 pandemic on the working of healthcare workers. The impact of the COVID-19 infection on the clinical examination and various surgical procedures, particularly in Otolaryngology is summarized in this paper. In this literature review, we have also discussed the strategies to prevent COVID-19 infection in healthcare workers during their routine handling of general and COVID-19 patients. To write this review, an extensive search and analysis of the literature was done based on strategies to prevent COVID-19 in healthcare workers, while dealing with COVID-19 patients.

**KEYWORDS :** COVID-19, Coronavirus, Pandemic, Healthcare workers

### INTRODUCTION:

Since its evolution in Wuhan, China in December 2019, COVID-19 has posed an extraordinary threat to the global population. Approx. 45, 97, 894 cases of COVID-19 have been detected including 311 588 deaths as of 17 May 2020, since the first case was reported on 31<sup>st</sup> December, 2019.<sup>1</sup> It has rapidly spread throughout the world following an exponential growth, leading to many casualties. It was classified as Pandemic by WHO (World Health Organization) on March 11, 2020.<sup>2,3,4</sup> The COVID-19 pandemic has had a substantial effect on the health care systems around the globe. Due to this, the world has come to a halt as it has led to mental, economic and physical impact on everyone. The virus spreads via the small droplets that emerge from the nose or mouth, when a person infected with COVID-19 speaks, coughs or sneezes. Infection can also spread via the surface or objects that have the virus on it, if the person touches their eyes, nose or mouth after touching these surfaces and objects.

Due to the lack of protective materials and rapid transmission of the disease, the prevention and control of disease are facing great challenges. With SARS-CoV-2 outbreak being highly transmissible, it became evident that the health care systems from all around the world need to be reformed and new strategies have to be evolved to minimise the risk of disease transmission. However, when these pandemic wanes and the curve flattens, a surge in patients visiting the hospitals is expected which were previously restricted and were managed conservatively. Looking forward towards positive side, public health systems need to consider as how they can provide the best and effective management to the patients by minimising the risk of transmission to patients as well as the health care workers in post-acute stages of COVID-19.

We summarize our prevention strategies from various literatures provided, through which we hope might help other ENT units to formulate their control plans to prevent nosocomial transmission of COVID-19.

### Structure of virus and its pathophysiology:

SARS-CoV-2 is a single stranded RNA enveloped virus, 50-200nm in diameter and is derived from beta coronavirus family (SARS-CoV2).<sup>5</sup> The RNA genome is 30 Kb, with one vital

encoded structural protein, spike glycoprotein (S), which consists of three S1-S2 hetero-dimers which binds to angiotensin converting enzyme-2 (ACE 2) receptor on type II pneumocytes.<sup>6,7</sup>

The SARS-CoV-2 enters the type II pneumocytes via endocytosis and multiplies in the cytoplasm. Stress induced by the viral protein upon the type II pneumocytes leads to apoptosis of these cells. Also, the SARS Cov-2 RNA acts as a pathogen associated molecular pattern (PAMP), which is recognised by the pattern recognition receptors or toll like receptors, leading to surge in chemokines causing neutrophil migration and activation, finally leading to destruction of the alveolar-capillary walls.<sup>7</sup>

### Mode of transmission:

This virus can be transmitted through droplet transmission, fomites, conjunctiva and feco-oral route.<sup>8,9</sup> Also, it has been found that local transmission can occur through affected patients body fluids such as saliva, respiratory droplets, aerosols, urine and faeces.<sup>8</sup> It has been noted that these viruses get stabilised at lower temperatures i.e., at 4 degree Celsius, it has higher survival rate.<sup>10,11</sup> Any symptomatic patient can shed the infection throughout his clinical course, prior to his presentation of symptoms and also during his symptomatic course and recovery period.

### Half-life of SARS-CoV-2 on various objects<sup>12</sup>:

Aerosols	1.5 hrs
Copper	1 hr
Cardboard	3.4 hrs
Stainless steel	5.6 hrs
Plastic	6.8 hrs

### Viable residing time of SARS-CoV-1:

Aerosols	3 hrs
Copper	4 hrs
Cardboard	24 hrs
Stainless steel	48 hrs
Plastic	72 hrs

The risk of contamination in upper respiratory tract examination is very high. In previous studies conducted in China, SARS-CoV-2 was detected in 63% of nasopharyngeal

swabs, 46% of the fiberopticbronchoscopy brush biopsies and 193% of Broncho-alveolar lavage fluid specimens.<sup>13,14</sup> Higher viral loads were detected in the nose and the nasopharynx area than in the throat after the onset of symptoms of COVID-19<sup>13</sup>

**Clinical Presentation of COVID-19 patient:**

This virus called SARS CoV-2 causes an infection called COVID-19 (coronavirus disease),<sup>15</sup> which presents similar to influenza virus like flu in varying number of symptoms. In both these infections, the clinical course can vary from asymptomatic to severe pneumonia.

According to the clinical studies, the most common symptoms consists of cough mostly dry cough, high grade fever, shortness of breath, muscle pain, bone pain, headache, diarrhoea, nasal discharge, and sore throat.

Most common symptom in covid-19 patients is fever, but only around 45% patients are febrile during their early presentation. They also present with cough, which may be associated with or without sputum.<sup>16</sup> Patients also presents with complaints of respiratory symptoms like dyspnoea, sore throat, nasal congestion or constitutional symptoms like malaise, chills, headache, nausea or vomiting.<sup>16-19</sup> If presented late, it can also result in acute respiratory distress syndrome (ARDS), which later can worsen and might precipitate septic shock.

**Case definition of SARS-CoV-2 Infection: (According to WHO) Suspected case of COVID -19:**

A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath

AND with no other aetiology that fully explains the clinical presentation

AND a history of travel to or residence in a country/area or territory reporting local 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 a contact with a confirmed or probable COVID-19 case in the last 14 days prior to the onset of symptoms

OR

A patient with acute severe respiratory infection (fever and at least one sign/symptom of respiratory disease e.g., cough, shortness of breath)

AND requiring hospitalisation

AND with no other aetiology that fully explains the clinical presentation

**Probable case:**

A suspect case whose COVID-19 test is inconclusive

**Confirmed case:**

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

**Screening criteria of COVID-19 by CDC:**

Clinical Features	Epidemiologic Risk (within 14 days of symptom onset)
Pyrexia OR Respiratory symptoms (cough, dyspnea, sore throat, and nasal congestion)	AND Close contact with RT-PCR confirmed COVID-19 patient
Pyrexia AND Respiratory symptoms (cough, dyspnea, sore throat, and nasal congestion) requiring hospitalization	AND History of travel to CDC flagged areas
Pyrexia AND Severe Respiratory illness (pneumonia, ARDS) requiring hospitalization AND without any alternative diagnosis	AND No discernment of exposure history

**Diagnosis and management:**

The confirmation of the diagnosis of SARS CoV-2 infection is carried out by specific tests which are advocated by WHO.<sup>20</sup>

Any suspected person fulfilling the criteria of suspected case should be tested for SARS CoV-2, where samples are collected from both oropharynx and nasopharynx.<sup>21, 22</sup> After sample collection, serological tests employs enzyme linked immunosorbent assay (ELISA) or Western blots which detects specific COVID-19 proteins. Molecular approaches are established on Real Time-PCR (RT-PCR) or northern blot hybridization, targeting specific COVID-19 genes.<sup>23</sup> Viral antigens present are detected by using direct immunofluorescent assay (IFA).

The viral research institution in China has conducted a basic identification of the SARS-CoV-2 via the classical Koch's postulates and also observing its morphology through electron microscopy.<sup>24</sup> Depending on the individual stage of the disease, immunity of an individual, the individual incubation period or even the quality of the swab collection, false-negative results are possible.

According to previous data analysis, around 80% of COVID-19 cases take a mild course and these patients recover well especially in young age group, whereas 15% of patients are seriously ill and require intensive care.<sup>25,26</sup> However, more than 80% of the cases could also remain asymptomatic and go undetected because they were not tested.

The current analysis of the various studies brings to a conclusion that most serious illness and deaths occur in the older population. Patients with comorbidities and chronic illness, especially chronic lung diseases such as COPD, asthma, any cardiac illness, hypertension, increased BMI, chronic kidney failure, diabetes mellitus, etc represent a high-risk group.<sup>27,28</sup>

The basic management is predominantly supportive, amidst the absence of antiviral drugs. The most common presentation in COVID-19 patients is fever, non-productive cough and sore throat. Hence, the first line drugs used are paracetamol and antitussives.<sup>17</sup> In cases of severe respiratory distress, supplementary oxygen at 5L/min must be administered and the oxygen target must be more than 92-95% in pregnant patients and more than 90% in other patients.<sup>29</sup>

Complications such as septic shock and acute kidney injury (AKI) should be managed according to sepsis protocol and renal replacement therapy (RRT).<sup>17</sup> Appropriate empiric antimicrobial coverage must be provided if patients develop superimposed bacterial or fungal infection in clinical course of COVID-19. Also, in patients who develop hypoxia refractory to supplemental oxygen, WHO recommends use of extracorporeal membrane oxygenation (ECMO).

Public health plays a pivotal role in controlling the infection of COVID-19. The main objective of COVID-19 management rests on basics of social distancing to limit the rapid emergence of new cases by transmission. This concept is referred to as "flattening the curve" in epidemiological context.

**Vaccination:**

There has been a considerable amount of global investment, resources and effort towards development of a vaccine. Unfortunately, vaccine for COVID-19 hasn't been developed yet.

One of leading vaccine developers, Moderna Tx Inc (Cambridge, MA, USA), has phase I, open label, dose ranging

clinical trials going on to evaluate its safety profile, reactogenicity and immunogenicity in healthy subjects.<sup>30</sup> Many efforts have been directed to develop vaccines against SARS CoV infections in recent decades, but a limiting factor is the degree of cross-protection rendered by these vaccines due to their extensive sequence diversity.<sup>30,31,32</sup>

#### Drugs used:

- **Remdesivir:** It is a nucleoside inhibitor which is by far the most secure drug against COVID-19 treatment. It is a monophosphoramidate prodrug which causes premature termination of the viral RNA replication. Currently, suggested dosing is a 10 days course, i.e. 200 mg for first day followed by 100 mg i.e. for rest nine days.<sup>33</sup>
- **Lopinavir and Ritonavir:** These are the protease inhibitors which are used in combination in HAART regimen in the treatment of HIV. This combination has shown to be effective against SARS in vitro.<sup>34</sup> Current Chinese guidelines for treatment of COVID-19 includes per orally 50mg-200 mg BID dose for 10 days.<sup>35</sup>
- **Umifenovir:** It is a non-nucleoside broad spectrum antiviral, membrane fusion inhibitor, which is used in treatment and also for prophylaxis of influenza in Russia and China, yet to be approved by FDA. Dose is 200mg TDS for 10 days.
- **Chloroquine:** it is an anti-malarial drug and in viruses, it has a peculiar mechanism of action wherein it inhibits Ph-dependent stages of replication and this immunomodulation is dependent on cytokines (IL-6 and TNF- $\alpha$ ) suppression of production and dissemination. Also, in monkey cell line experiments (Vero E6), it has been seen that chloroquine interferes with the receptor glycosylation and hence affects the SARS CoV-2 entry mechanism. In another in vitro study, it has been seen that hydroxychloroquine had a higher potency in comparison to chloroquine at inhibiting the SARS CoV-2 infection. Dose for hydroxychloroquine is 400 mg BD for the first day followed by 200 mg BD for next four days.<sup>33</sup> Also, hydroxychloroquine can be given for pre-exposure prophylaxis and post-exposure prophylaxis in an individual e.g., healthcare workers with documented exposure to SARS CoV-2.<sup>36</sup>
- **ACE inhibitors and Angiotensin receptor blockers:** Since SARS-CoV-2 enters the type II pneumocytes via the ACE 2 receptor, which is a functional receptor, this ACE 2 receptor has a reciprocal physiological action on ACE 1. It then converts the angiotensin II back to angiotensin I. In contrast, patients taking ACE 1 will have low levels of angiotensin II.<sup>37-39</sup>
- **Antipyretics:** First line antipyretic is acetaminophen. Some studies have shown that ibuprofen upregulates ACE 2 receptors.<sup>40,41</sup>
- **Systemic corticosteroids:** The use of corticosteroids in the management of ARDS, secondary to pneumonia is still controversial. The reason behind this approach is that they prolong the viral shedding time and maintain a systemic anti-inflammatory state which will further minimise the disease process of ARDS, or severe pneumonia.

Since there is no definitive vaccination and sure shot cure for this SARS CoV-2 infection at present, the most effective intervention is social distancing which will help one to stay confined and healthy as well as break the chain of transmission, helping the vulnerable population from acquiring infection during this pandemic. The goal of lockdown was  $R < 1$ . The main motive behind this lockdown was to reduce the number of people getting infected by a COVID-19 positive patient. If herd immunity is achieved, then the epidemic will subside.<sup>42,43</sup>

With many in-depth studies and research is still undergoing for the effective vaccine and treatment for COVID-19, the

present day safest and prudent measure is social distancing, hand hygiene and respiratory hygiene.

#### Strategies for prevention of spread of COVID-19 in health care workers:

Health care workers are at high risk of exposure to COVID-19. Hence it is crucial to ensure the safety of health care workers so as to ensure they do not contract the disease and also to safeguard the patient care.

The strategies for infection control against COVID-19 includes: material preparation and circulation, Education and training on infection prevention measures, a triage strategy, limiting out patients number in the hospital, restructuring of hospital departments, and keeping the environment clean, etc.

#### Implementation of triage method:

**1. Pre-test:** In order to lighten the patient load with patients visiting hospitals with fewer symptoms and to reduce the risk of cross-infection, hospitals have set up flu clinics, where primary level physician can perform pre-examination and segregate the patients according to their symptoms. During this pre-examination, patients' needs to be thoroughly inquired about their clinical symptoms, area residing, any contact history with infected persons and body temperature measurement for early identification of the potentially infected people.

**2. Home visit:** In view to prevent community spread of the disease, through various channels, the primary health care workers along with other health care workers, needs to carry out on-site visits, distribute health brochures, educate the common people about the symptoms and reporting to hospital immediately in case of suspected clinical symptoms.

**3. Follow-up:** Next, to decrease the density of out patients visiting the hospitals, all the departments should build a separate waiting area from the treatment area, reduce the number of appointments, schedule appointments online at different times, and increase telemedicine consulting services. In addition, taking account that the median age of COVID-19 patients was 59 years and that morbidity and mortality is greater in the elderly, HCWs >65 years were suspended from outpatient activities.<sup>44</sup>

Also, on the wards, temperature monitoring can be set at the entrance for all persons, an epidemiological history should be taken from all patients and caregivers, and everyone on the ward should be encouraged to wear a surgical mask.<sup>44</sup>

#### Precautions to be taken for surgeries:

Elective surgery needs to be initially suspended until the control measures are established, and then gradually can be restarted after getting familiar with the new safety precautions. Also, in the case of emergency, patient can be operated after taking COVID-19 sample and all the surgeons and physicians scrubbing for that case needs to be extra-cautious and must be kept in quarantine, until the viral report of the patient comes.

Post-surgery, patients with suspected COVID-19 should be transferred to a negative pressure isolation ward and kept there, till their COVID-19 report comes. Those with negative report should be returned to their respective department, whereas those who test positive must be transferred to the COVID ward for further management and treatment.

It should be highlighted that fever occurs in only 43.8% of patients with COVID-19 on initial presentation. Hence, many patients may be missed, if focus is kept only on fever detection for suspected cases during preoperative screening.<sup>16</sup>

Therefore, CT-scan needs to be advised pre-operatively on elective surgical patients, along with virological testing for COVID-19 in suspected patients.<sup>16</sup>

In specialities like ENT, where the risk of aerosol generating procedures are high, special measures have to be taken before posting any surgical case. Thus, to manage the risks associated with ENT procedures, open-type suction should be replaced by closed suction for surgical patients. Suction should be used before tracheal nursing in order to minimize sputum production during the procedure. Aerosol inhalation should be replaced by in-tube infusion or spray humidification to humidify the trachea.

#### Applying standard precautions for all:

1. Appropriate hand hygiene by hand washing with simple soap and water or an alcohol-based hand rub for at least 20 seconds and also appropriate use of gloves to break the chain of transmission from one patient to another by health care worker's contaminated hands.<sup>45,46</sup>
2. Appropriate disinfection and cleaning of the environment surfaces and equipment used for the care of the patient to diminish transmission rate by the indirect fomite route.
3. Usage of appropriate personal protective equipment's such as gowns, masks, goggles, N95 respirators to diminish the exposure of health care workers to infectious agents.<sup>47</sup>
4. Appropriate management of hospital waste and used linens to reduce environmental contamination rate.
5. Cough etiquette to minimise droplet transmission.

#### Implementing empiric additional precautions- contact and droplet precautions:

- In supplementation to using standard precautions, all individuals and HCWs should follow contact and droplet precautions before entering the room of suspected or confirmed COVID-19 patients.
- All suspected and infected patients should be allotted adequately ventilated single rooms. For general ward rooms with natural ventilation, adequate ventilation is considered to be 60 L/s per patient.<sup>47</sup>

These are the few strategies which will help in reducing the chances of transmission as well as exposure in the health care setting.

Standard precaution measures are hereby instructed to reduce the potential transfer of microorganisms from one person to another, whether symptomatic or asymptomatic. Specific transmission- based precautions are needed to be implemented when handling suspected patients.

- Distance of at least 1 metre between each patient's beds, regardless of whether they are suspected or confirmed cases of COVID-19, should be maintained.
- Disposable equipments should be used, if possible. If dedicated equipments like stethoscopes, blood pressure cuffs and thermometers need to be shared among the patients, then cleaning and disinfecting these equipments before using for each individual patient (by ethyl alcohol 70%) should be followed.<sup>48,49</sup>

#### Administrative measures related to health care workers:

- Arrangement of adequate training for all health care workers.<sup>49,50</sup>
- Safeguarding the treating health care workers by ensuring an adequate patient-to-staff ratio
- Creating a surveillance process for acute respiratory infections
- Ensuring that HCWs and the public understand the importance of promptly seeking medical care

- Monitoring the overall HCWs compliance to maintain the standard precautions and also providing mechanisms for improvement as needed and required.

#### Benefits of Lockdown<sup>50</sup>:

Lockdown is beneficial at all 3 extents: local extent, national extent and global extent.

At the local extent, people infected will be minimised and hence the health care system is not excessively exhausted. At the national extent, it obtains critical time required for capacity building of health care (testing and tracing; protective equipment, case management) to respond the epidemic.

At the global extent, it will steady the pandemic and enable global resources to tackle the epidemic at the source.

The aim of social distancing is to reduce the spread of COVID-19. Hence, it works by the attempting to slow down the disease transmission process by maintaining adequate physical distance between people and thus reducing social interactions. This in turn helps the health care systems by avoiding the overburdening of cases, a strategy now widely known as "flattening the curve".<sup>42</sup> This flattening of curve means a decrease in the number of affected persons at the height of the epidemic and thus distributing the cases over a longer time frame. This can be achieved by reducing the reproduction number (R), which means the number of affected individuals by each carrier.<sup>42,43</sup>

Post-lockdown flare-ups are more easily controlled with geographically focused efforts when they remain local longer. Long term surveillance and management of COVID-19 crisis is needed with both public health and also by taking care of the economic, social, and psychological trauma that it will leave on the population.

#### Post Lockdown protocols<sup>50,51</sup>:

**1. Social distancing:** One of the most important step to interrupt the transmission chain and minimise the rate of transmission is practicing social distancing (distance of 2 metres). This must be enforced at all public places e.g., grocery stores, govt. and private offices, departmental stores, banks, health care centres etc.

**2. Face mask:** Another effective measure to reduce the risk of infection is by strict implementation of usage of face mask.<sup>47,49</sup>

**3. Screening of high-risk population:** Regular screening of all vulnerable people which includes elderly people (above 60 years) and also those with comorbidities must have to be done. They shall have to remain at home or work from home, if possible.

**4. Outpatient care:** Routine outpatient services can be started with limited number of patients and only those with genuine symptoms. All non-COVID hospitals should have a fever screening OPD, ensuring social distancing at all times.

**5. Role of telemedicine:** Keeping in view of social distancing, utilisation of telemedicine and technology should have to be expanded and widely promoted.

**6. Training and capacity building:** In consideration of the health care workers and hospitals being affected leading to quarantining/sealing, continuous training and capacity building of the budding health care professionals is must to combat any emergency situation with the help of the trained manpower.



**7. Sample pooling:** It can be used as a strategy to detect the community transmission of SARS-CoV-2.

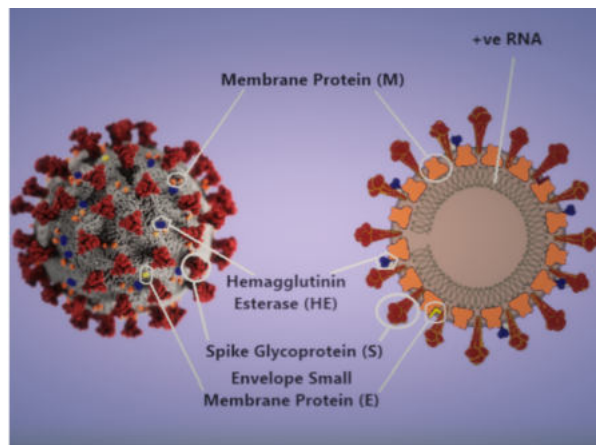
**8. Testing:** The most important step post-lockdown is a meticulously planned strategy for massive testing in the community. Testing should be done on priority basis, firstly for all high-risk people like migrant workers, close household contacts, health care workers etc. followed by low-risk people.

**9. Strong contact tracing and testing:** Since there is no definitive cure or vaccine developed yet for COVID-19, the government should strictly test, trace and quarantine all the suspects to further reduce the community transmission post-lockdown, since people with COVID-19 were found to be most infectious to others prior and within 5 days of onset of symptoms. Within 5 days of onset of symptoms, the attack rate was 1.0% (95% CI, 0.6%-1.5%), whereas those with pre-symptomatic exposures, the attack rate was 0.7% (95% CI, 0.2%-2.4%).<sup>52</sup>

**CONCLUSION:**

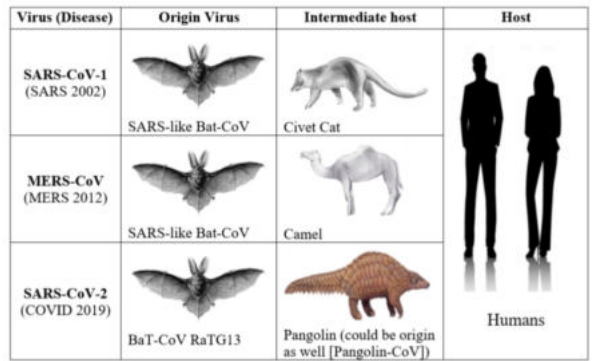
This review is intended to help the readers understand about the pathophysiology of COVID-19 and the strategies and measures required to curb COVID-19 infection post lockdown which should be practiced worldwide and also suggested about the future directions that the global community should take to manage and mitigate this emergency situation. The strategic approach would be innumerable rampant testing, strong contact tracing, isolation and follow-up. In a developing and low income country like India, this will mean bargaining to achieve a complex balance between stopping the spread of SARS-CoV-2, and granting freedom to people for their sustenance, before they slip into extreme poverty and suffering. Other various measures that can strengthen counter measures for this pandemic are rapidly updating epidemiologic data, free availability of accredited information, and a multidisciplinary approach that bridges the gap in knowledge between basic sciences and clinical sciences.

This literature review comprehensively helps us in summarizing the most relevant studies relating to the individual strategies that influence the clinical course and management of COVID-19. Due to the lack of available and validated therapeutics, most of the counter measures, at present, rely on the usage of public health containment and quarantine approaches. Hence, there is a need to upgrade and increase investments towards research and development of newer management strategies for COVID-19.



**FIGURE 1:** 3-D model of the SARS-CoV-2 virion and a schematic diagram of its structural proteins and genome.

Image component modified from CDC Public Health Image Library (ID 23312: Alissa Eckert and Dan Higgins)



**Fig 2:-** Transmission chain of major coronaviruses regarding its natural reservoir, intermediate host and target

**Table 1:-** Summary of ongoing clinical trials for immunoprophylaxis

Number	Title	Interventions	Age	Intervention model	Masking	Start date	Completion date	Locations
1. NCT0429721	Safety and Immunity of Covid 19 aPC vaccine	Biological: pathogen specific aPC	6 months to 80 years	Single arm clinical trial	Open label	February 15, 2020	December 31, 2024	Guangdong, China
2. NCT0427086	Immunity and safety of Covid 19 genetic antigenic vaccine	Biological: injection and injection of V-SM2NP-DC vaccine and antigen-specific CTLs	6 months to 80 years	Single arm clinical trial	Open label	March 21, 2020	December 31, 2024	Guangdong, China
3. NCT0425541	Safety and immunogenicity study of 2019-nCoV vaccine (mRNA-1273) to prevent SARS-CoV-2 infection	Biological: mRNA-1273	18 years to 35 years	Non-randomized trial	Open label	March 3, 2020	June 1, 2021	United States
4. ChiCTR20090	A phase I clinical trial for recombinant novel coronavirus (adenoviral vector)	Recombinant novel coronavirus vaccine (adenoviral vector)	18 and 60 years	Non-randomized trial	Open label	March 16, 2020	December 31, 2020	Hubei, China

**Table 2: summary of ongoing trials for chemoprophylaxis**

Number	Title	Interventions	Age	Allocation	Masking	Start Date	Expected Completion Date	Locations
1. NCT0430653	Treatment of COVID-19: Care and Chemoprophylaxis of Contacts as Prevention	Antiral treatment and prophylaxis or Standard Public Health measures	≥ 18 years	Randomized	Open Label	March 18, 2020	June 15, 2020	Barcelona, Spain
2. NCT0431844	Hydroxychloroquine Post Exposure Prophylaxis for Coronavirus Disease (COVID-19)	Hydroxychloroquine or Placebo	≥ 18 years	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Mar 20	Mar 22	New York, United States
3. NCT0431815	Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact With COVID-19 Patients (PHYRA Trial)	Hydroxychloroquine or Placebo	≥ 18 years	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	April 1, 2020	March 31, 2021	
4. NCT04251871	Treatment and Prevention of Traditional Chinese Medicines (TCMs) on 2019-nCoV Infection	Oxygen therapy, alpha-interferon via aerosol inhalation, and lopinavir/ritonavir and Traditional Chinese Medicines (TCMs) granules	14 Years to 80 Years	Randomized	Open Label	January 21, 2020	January 22, 2021	Beijing, China
5. NCT04305047	Chloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting	Chloroquine or Placebo	≥ 18 years	Randomized	Double (Participant, Investigator)	May 20	May 22	Oxford, United Kingdom
6. NCT04311174	COVID-19 Ring-based Prevention Trial With Lopinavir/Ritonavir	Drug: Lopinavir/ritonavir	≥ 18 years	Randomized	Masking: Single (Outcomes Assessor)	March 30, 2020	March 31, 2022	Ontario, Canada
7. NCT04312240	NO Prevention of COVID-19 for Healthcare Providers	Drug: Inhaled nitric oxide gas	18 to 99 Years	Non-Randomized	Masking: None (Open Label)	March 20, 2020	March 20, 2022	Boston, United States
8. NCT04306048	Post-exposure Prophylaxis for SARS-Coronavirus 2	Hydroxychloroquine or Placebo	≥ 18 years	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	March 17, 2020	May 21	Massachusetts, United States

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