

# COVID-19 a Serious Health Issue - A Literature Review of Various Journal around the World

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**Abstract:** COVID-19 is an infectious disease which is caused by nCoV belongs to the  $\beta$ -coronavirus genus. It is proposed that the major host for alphacoronaviruses and betacoronaviruses are Bats It's transmitted from infected person who has symptoms from virus including cough and sneezing, to susceptible person via airborne, zoonotic droplet nuclei. Due to the absence of specific Vaccine and Antiviral drug Epidemiological reports suggest that the morbidity and mortality rate is drastically increasing day by day. The common clinical symptoms include fever, sore throat, cough, myalgia, headache, fatigue, and breathlessness or dyspnea. Infection is confirmed by positive test to SARS-CoV-2 by real-time RT-PCR, In India it is done in National Institute of Virology in Pune. Some drugs shows invitro efficacy against Novel Coronavirus ("2019-nCoV") i.e. chloroquine and hydroxychloroquine (Antimalarial Drugs), Liponavir and Ritonavir (HIV protease inhibitor). Supportive therapy include Azithromycin, Tocilizumab, some Immunomodulators and NSAIDs. Some safety measure should also be taken like wash your hands with soap, use sanitizers, cover your outh with elbow during cough or sneeze.

**Keywords:** Coronavirus Disease (COVID-19), Acute Respiratory Distress Syndrome (ARDS), Coronaviruses (COVs), Severe Acute Respiratory Syndrome (SARS), Middle East respiratory syndrome related coronavirus (MERS-CoV), Chinese Centre for Disease Control and Prevention (CCDC), World Health Organization (WHO), Novel Coronavirus ("2019-nCoV")

## 1. Introduction

According to WHO, COVID-19 is an infectious disease which was unknown before the outbreak began in wuhan city of china in December 2019. This disease is caused by recently discovered virus called coronavirus.

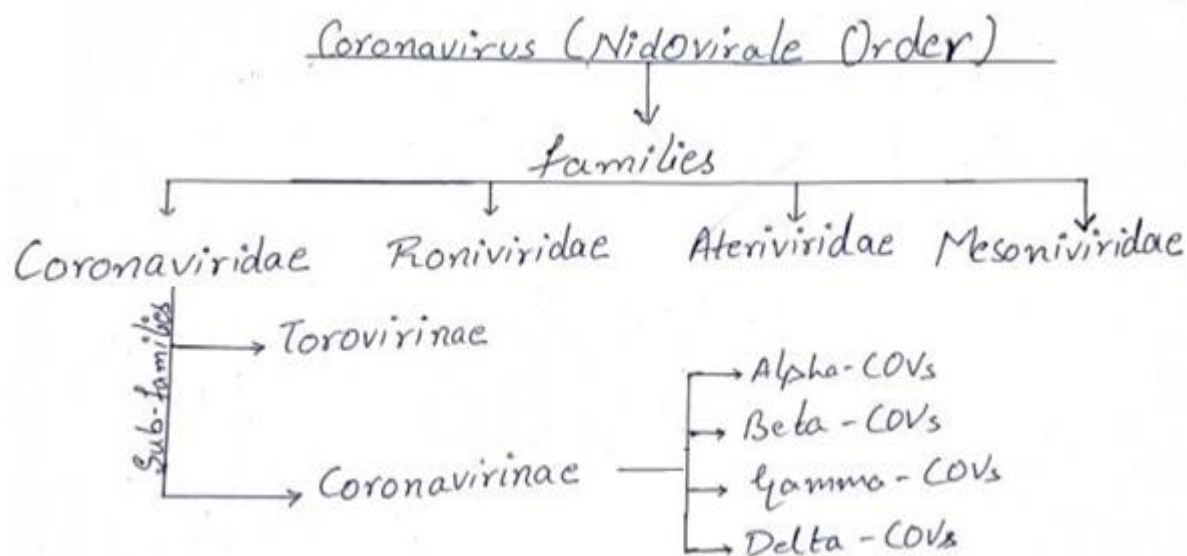
### 1.1 Coronavirus

Coronaviruses (COVs) are the type of positively sensed enveloped RNA viruses, having club-like spikes on their surface, a large RNA genome, with size ranging from 60 nm to 140 nm in diameter and having a unique tendency to replicate. Coronaviruses (COVs) are special type of viruses having Nidovirales order, which include families i.e.

Coronaviridae, Roniviridae, Mesoniviridae, and Ateriviridae. All viruses in Nidovirales order are single strand positively sense RNA viruses.

CoVs are divided into four genera:  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -coronavirus. Where  $\alpha$ - and  $\beta$ -coronaviruses only infect mammals, whereas  $\gamma$ - and  $\delta$ -coronaviruses mainly infect birds, with a few infecting mammals.

Human CoVs include  $\alpha$ - coronaviruses (229E and NL63),  $\beta$ - coronaviruses (OC43 and HKU1), the Middle East respiratory syndrome related coronavirus (MERS-CoV), severe acute respiratory syndrome-related coronavirus (SARS-CoV), or 2019-nCoV. The 2019-nCoV belongs to the  $\beta$ -coronavirus genus.



The rate of Recombination of Coronaviruses are very high because there is a development of transcription error and RNA Dependent RNA Polymerase (RdRP) jumps.<sup>(3)</sup>

As the mutation rate is very high and the Coronaviruses are pathogens which are zoonotic in nature, present in both humans and various animals with a clinical features ranges

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from asymptomatic to the urgent requirement of Hospitalization in its intensive care unit;<sup>(4)</sup>

Coronaviruses causes infection (disease) in various system in animal's body i.e. Respiratory Gastrointestinal and Neurological system, but in Humans the Coronavirus (COVs) is only associated with Respiratory Tract illness or Respiratory Tract Infection and an oral fatal Lung disease. The most pathogenic corona virus is SARS-COV that is responsible for Severe Acute Respiratory Syndrome (SARS), in Humans.<sup>(5,6,7)</sup>

In past few years, the number of coronaviruses have been identified in wide variety of Bat's species throughout, Asia, Europe, Africa and America.<sup>(7a)</sup>  $\alpha$ - coronavirus,  $\beta$ -coronavirus mainly infect mammals, 7 out of the 15 currently assigned viral species have only been found in bats.<sup>(7b)</sup>

It is proposed that the major host for alphacoronaviruses and betacoronaviruses are Bats and play an important role in evolution of these two genera of Coronaviruses.<sup>(7c)</sup>

Some research suggests that Bats are associated with high profile human diseases i.e. Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).<sup>(7d)</sup>

The causative agent was identified from throat swab samples conducted by the Chinese Centre for Disease Control and Prevention (CCDC) on 7th January 2020, and was named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The disease was named COVID-19 by the World Health Organization (WHO).<sup>(8)</sup>

Whole world is watching the outbreak of COVID-19, in the form of pneumonia of unknown etiology was reported in Wuhan, Hubei province, china in December 2019, which were later proven to be caused by a novel coronavirus (named as "2019-nCoV"),<sup>(9)</sup>

### Pathophysiology

Structurally, the SARS coronavirus (SARS-CoV) has a well-defined composition. It comprises of 14 binding sites that directly interact with human angiotensin-converting enzyme 2. Of these amino acids, 8 have been conserved in SARS-CoV-2. In humans, coronaviruses were thought to cause mild respiratory infections until the identification of SARS-CoV and Middle Earst Respiratory Syndrome coronavirus (MERS CoV). Although there's an unknown exact pathophysiological mechanisms underlying the emergence of SARS-CoV-2 because of pending trials, genomic similarities to SARS-CoV could help to explain the resulting inflammatory response which lead to severe pneumonia.<sup>(10)</sup> Until these clinical trials are initiated, the exact mechanism of SARS-CoV-2 is unknown or remains hypothetical.

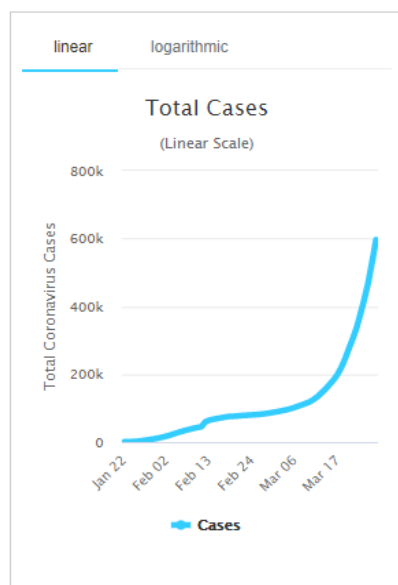
### Mode of Transmission

As the virus is zoonotic in nature but there is drastic increase in the number of cases of those patients, who didn't visit Animal Market of Wuhan, therefore it is confirmed that this virus spreads by human to human transmission of CORONA.<sup>(11)</sup>

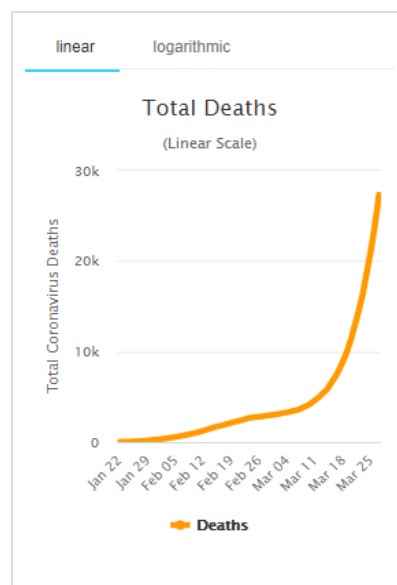
It is transmitted from infected person who has symptoms from virus including cough and sneezing, to susceptible person via airborne, zoonotic droplet nuclei. Virus was replicated in ciliated epithelium that caused cellular damage and infection at infection site. According to an article which was published in 2019, Angiotensin converting enzyme 2 (ACE.2), a membrane exopeptidase in the receptor is used by corona virus in entry to human cells.<sup>(12,13,14)</sup>

### Epidemiology

As of today, 28th March, 2020, there are 597627 Coronavirus cases, with 27365 deaths, while 133363 has been recovered. very interestingly the highest number belongs to Italy i.e. 9,134 deaths. The death toll is followed by Spain (5,138), china (3,295) and Iran (2,378) and this number is drastically increasing.

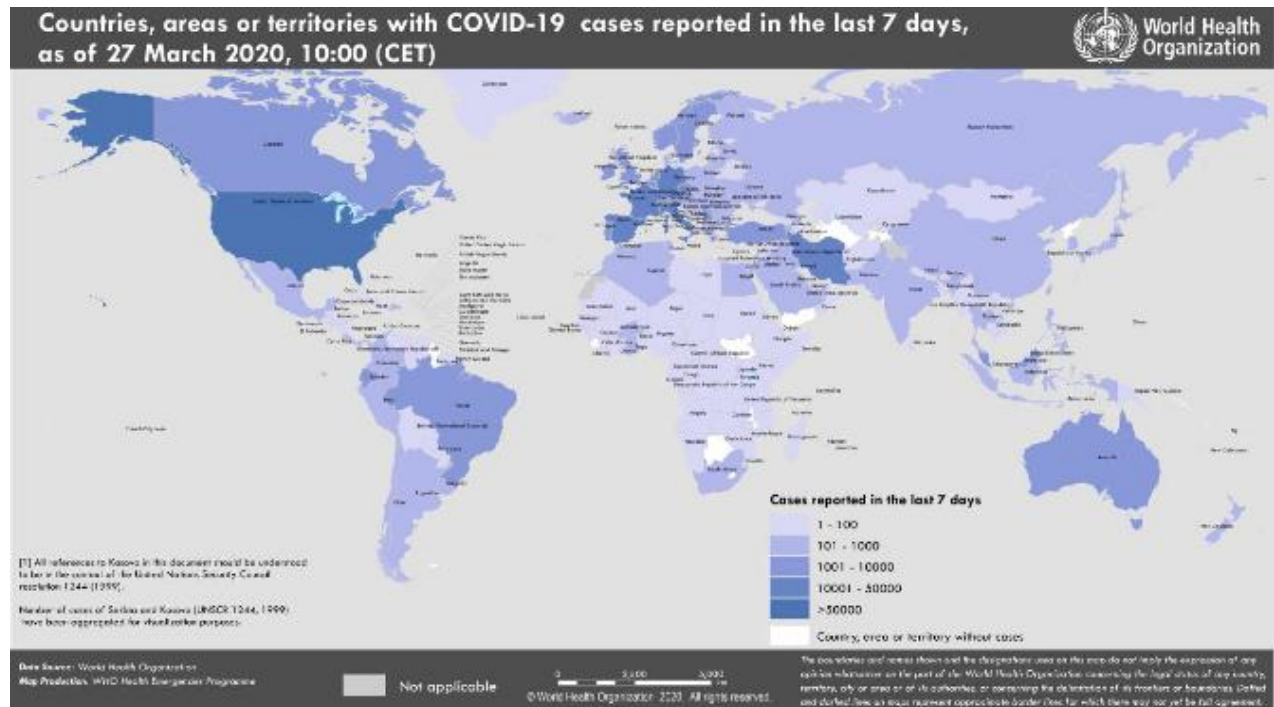


[More Case Statistics](#)



[More Death Statistics](#)

(15)



Countries, territories or areas with reported confirmed cases of COVID-19, 27 March 2020.<sup>(16)</sup>

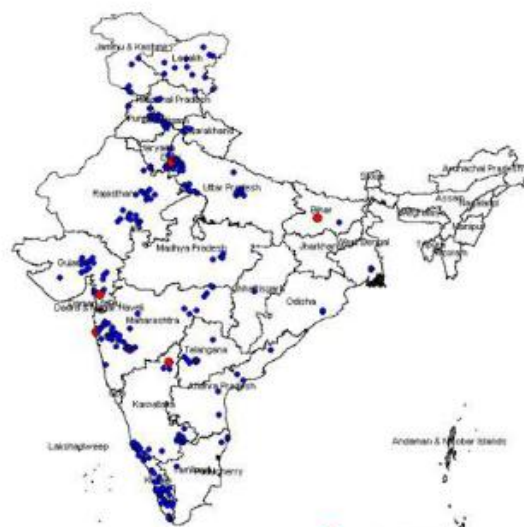
### COVID-19 cases – India

(as on 22/03/2020, 06:30 PM)

State	Total Cases	Death
Maharashtra	67	2
Kerala	52	
Delhi	29	1
Uttar Pradesh	27	
Karnataka	26	1
Rajasthan	24	
Telangana	22	
Haryana	21	
Punjab	21	1
Gujarat	18	1
Ladakh	13	
Andhra Pradesh	5	
Chandigarh	5	
Jammu & Kashmir	4	
Madhya Pradesh	4	
Tamil Nadu	7	
West Bengal	4	
Uttarakhand	3	
Biher	2	1
Himachal Pradesh	2	
Odisha	2	
Chhattisgarh	1	
Puduchery	1	
<b>Total</b>	<b>360</b>	<b>7</b>

Source: <https://www.mohfw.gov.in/>

Location of cases within states is shown as per district information available



1 dot represent one case or death

(15)

On the basis of data which include 7,2314 confirmed, suspected and asymptomatic cases published by china CCDC on 17 February 17 in Chinese Journal of Epidemiology 80.9% of cases of COVID-19 are mild (with flu-like symptoms), and these can recover at home.

13.8% are cases are severe, developing severe diseases like pneumonia and dyspnea.

4.7% cases are very critical and can include: Respiratory failure, Septic shock, and Multi-organ failure.

In only 2% of cases which are reported showed that virus is fetal and Risk of mortality is more in elderly Patient. Comparitively very few cases are seen in children.<sup>(15)</sup>

#### Clinical Symptoms and Menifestation

Epidemiological data suggested that, the incubation period of 2019-nCoV ranges from 1 to 14 days, mostly ranging from 3 to 7 days.<sup>(16a)</sup>

Symptoms of COVID-19 are varied ranging from flu like symptoms, to ranging from asymptomatic state to acute respiratory distress syndrome and multi organ dysfunction. The common clinical symptoms include fever, sore throat,

cough, myalgia, headache, fatigue and breathlessness or dyspnea. Conjunctivitis has also been described.

So this COVID-19 is indistinguishable from other respiratory infections. Disease can progress to pneumonia, respiratory failure and death. This progression is associated with extreme rise in the level of inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNF $\alpha$ .<sup>(18)</sup>

In some patients - particularly the elderly and other with other chronic health conditions - these symptoms area easily develop into pneumonia, with chest tightness, chest pain, and shortness of breath (dyspnea).

COVID-19 starts with a fever, followed by a dry cough. After a week, it can lead to shortness of breath (dyspnea), with about 20% of patients requiring hospital treatment.<sup>(15)</sup>

### Diagnosis

First step of diagnosis is to confirm that weather the person made contact with people who are suffering from COVID-19 or visited China in Last few Days or Week.

A person is suspected if he's suffering from fever, sore throat and cough and having a history of direct contact with confirmed or suspected COVID-19's Patient.

Specific diagnosis is by specific molecular tests on respiratory samples (throat swab/ nasopharyngeal swab/ sputum/ endotracheal aspirates and bronchoalveolar lavage). Virus may also be detected in the stool and in severe cases, the blood.

### Commercial tests are also not available at present.

In India the suspected sample has to be sent to **National Institute of Virology in Pune**. Infection is confirmed by positive test to SARS-CoV-2 by real-time RT-PCR, isolation in cell culture of SARS-CoV-2 from clinical specimens, or rising serum antibody concentrations.

Other laboratory investigations are available but these are not specific this include:

- In the early phase of the disease, white blood cell count and platelet may be normal or decreased, with decreased lymphocyte count . There may be lymphopeni i.e. lymphocyte count <1000 has been associated with severe disease; liver enzymes, muscle enzymes, and myohemoglobin levels are increased in some patients.
- There is Elevation in C-reactive protein (CRP) level and erythrocyte sedimentation rates (ESR) but procalcitonin levels are usually normal. High level of procalcitonin reflects that there is bacterial co-infection.
- Elevated level of ALT/AST, prothrombin time, creatinine, D-dimer, CPK and LDH.
- High level of of ALT/AST, prothrombin time, creatinine, D-dimer, CPK and LDH reflects the severity of disease.
- The chest X-ray (CXR) usually shows bilateral infiltrates but may be normal in early disease.

- **The CT scan is more sensitive and specific.** CT imaging generally shows infiltrates, ground glass opacities and sub segmental consolidation.<sup>(20-21)</sup>

### Treatment

According to the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the FDA, there is no any specific medicine or vaccine which can use in the treatment and prevention of COVID-19 or SARS-CoV-2.<sup>(22,23,24)</sup>

### *Some Anti-Microbial & Anti-Viral Agents have tandency Against SARS-CoV-2*

#### Chloroquine:

Chloroquine belongs to Antimalarial class of drug Pre-clinical in vitro data suggested that chloroquine is effective against SARS-CoV-2.<sup>(25,26,27)</sup>

**Mechanism of Action:** MOA of chloroquine is not completely known.<sup>(58)</sup> But Researches suggested that it involves, inhibition of viral enzymes processes such as viral DNA and RNA polymerase, viral protein glycosylation, virus assembly, new virus particle transport, and virus release.

Other mechanisms may also involve Angiotensin Converting Enzyme 2 (ACE2) cellular receptor inhibition, acidification at the surface of the cell membrane which leads to the inhibition of fusion of the virus, and immunomodulation of cytokine release.<sup>(26,27,39,40,41,42,43)</sup>

#### Safety Measure:

There is Risk of prolongation of QT wave which leads to cardiac arrhythmias.

Risk of damage of Retina, especially with long term use.

Take Caution in patients who are suffering from G6PD deficiency.

Physician should take in account the Diabetic Condition of Patient.

There is no significant drug interactions.<sup>(28,29)</sup>

#### i) Hydroxychloroquine:

Hydroxychloroquine belongs to Antimalarial class of drug. There is Risk of prolongation of QT wave which leads to cardiac arrhythmias.

Pre-clinical in vitro data suggested that hydroxychloroquine is effective against SARS-CoV-2.<sup>(27,30,31,32,33)</sup>

**Mechanism of Action:** MOA of Hydroxychloroquine is not completely known.<sup>(58)</sup> But Researches suggested that it involves, inhibition of viral enzymes processes such as viral DNA and RNA polymerase, viral protein glycosylation, virus assembly, new virus particle transport, and virus release. Other mechanisms may also involve Angiotensin Converting Enzyme 2 (ACE2) cellular receptor inhibition, acidification at the surface of the cell membrane which

leads to the inhibition of fusion of the virus, and immunomodulation of cytokine release.<sup>(26,27,39,40,41,42,43)</sup>

#### Safety Measure:

Risk of damage of Retina, especially with long term use  
Take Caution in patients who are suffering from G6PD deficiency  
Physician should do dose adjustment in Diabetic Patient  
This drug have serious drug interactions.<sup>(29, 34)</sup>

#### ii) Lopinavir; Ritonavir:

Ritonavir and Liponavir belongs to the HIV Protease Inhibitor class of drug.

Pre-clinical in vitro data and study on animal show its efficacy against coronaviruses (SARS-CoV and MERS-CoV).<sup>(35,36,37,38)</sup>

Mechanism of Action: Lopinavir and Ritonavir works by potent inhibition of CYP3A4.<sup>(59)</sup>

It may also binds to Main Protease [M(pro)], a key enzyme for the replication of Coronavirus. This may suppress coronavirus activity.<sup>(44)</sup>

#### Supportive therapy:

##### i) Azithromycin

- It belongs Macrolide Antibiotic class of drug.
- Azithromycin is bacteriostatic, and macrolides may have immunomodulatory properties, so Azithromycin maybe used as adjunct therapy.<sup>(45,46,47,48,49)</sup>

**Mechanism of Action:** In pulmonary inflammatory disorders, Macrolides may have immunomodulatory properties. They may suppress inflammatory responses and reduce the excessive production of cytokines which is associated with respiratory viral infections; however, their direct effects on viral clearance is not clearly known. Immunomodulatory mechanisms suggested that Azithromycin reduces chemotaxis of neutrophils (PMNs) to the lungs by inhibition of cytokines (IL-8) and inhibition of mucus hypersecretion, decreased production of reactive oxygen species, increase neutrophil apoptosis, and activation of nuclear transcription factors is blocked.<sup>(46,47,48,49)</sup>

#### Safety Measure:

There is Risk of prolongation of QT wave which leads to cardiac arrhythmias.  
Some Significant drug interactions is also there.<sup>(50,51)</sup>

#### ii) Tocilizumab:

- Tocilizumab is a class of Interleukin-6 (IL-6) Receptor-Inhibiting Monoclonal Antibody
- Cytokine release syndrome may be a component of severe disease in COVID-19 patients.<sup>(52)</sup>

**Mechanism of Action:** Tocilizumab works by inhibiting IL-6-mediated signaling by competitively binding to both soluble and membrane-bound IL-6 receptors.

IL-6 is a pro-inflammatory cytokine that involves in T-cell activation, initiation of hepatic acute-phase protein synthesis, immunoglobulin secretion, induction and hematopoietic precursor cell proliferation and differentiation stimulation.

IL-6 is synthesized by various cells, which include T- and B-cells, lymphocytes, monocytes, and fibroblasts.<sup>(36)</sup>

A retrospective review analyzed 21 patients in which tocilizumab was added to standard therapy against COVID-19.<sup>(52)</sup>

**Safety Concerns:** There is a Risk of perforation of GI tract. Risk of hepatotoxicity. Special emphasis is given to the patients with thrombocytopenia and neutropenia. Hypersensitivity type of reaction that can occur shortly after administration.<sup>(53)</sup>

iii) **Other Immunomodulators:** Other immunomodulating agents alpha-interferon, sarilumab can be used as adjunctive therapy.<sup>(54,55)</sup>

iv) **Corticosteroids:** Corticosteroid therapy can not be recommended for viral pneumonia; however, use of corticosteroid may be considered for patients with refractory shock or acute respiratory distress syndrome (ARDS).<sup>(56)</sup>

v) **NSAIDs:** The FDA is investigating the use of NSAIDs in COVID-19's Patient. Acetaminophen may be used for temperature control in fever like condition. European Society of Intensive Care Medicine (ESICM), Society of Critical Care Medicine (SCCM) and Surviving Sepsis Campaign (SSC) recommendation suggested that acetaminophen can be prescribed for the control of body temperature (fever) in adults who are suffering from COVID-19.<sup>(56,57)</sup>

#### Protective Measure Against nCoV

- Wash your Hands with soap.
- Thoroughly clean your Hands with Alcohol based preparations or sanitizers.
- Maintain social distance i.e. atleast of 1 meter from another person.
- Avoid touching Nose, Eyes, and Mouth.
- Maintain Respiratory Hygiene i.e. cover your nose and mouth with your bent elbow during sneezing and coughing.
- If you have fever, cough or dyspnea kindly concern to the Medical Practitioner.
- Avoid direct contact with a person who is visited to the COVID-19 infected area in past 14 days.<sup>(60)</sup>

## 2. Conclusion

Corona virus spreads person to person via droplets through cough or sneeze, close contact with anybody should be avoided. Both infected and non -infected person should isolate them from each other. Heathy People should maintain good hygienic conditions and use preventive measure . If anyone is suffering from fever cough or sneezing he should consult Doctor. Some drugs can be used against COVID-19 e.g. Chloroquine, Hydroxychloroquine,

Liponavir, Ritonavir, Azithromycin, some NSAIDs and Corticosteroids etc.

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