

## COVID-19: A Global Pandemic

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### Abstract

### Review Article

COVID-19 is caused by novel  $\beta$ -coronavirus (SARSCoV2). It was first discovered in 2019, in Wuhan (seafood market), China. It was declared a global pandemic on 30<sup>th</sup> Jan 2020 by the WHO. Person to person transmission via respiratory droplets is source of infection. The incubation period is 2 weeks from exposure. Middle aged and elders >70 years age or people with co-morbid conditions like Diabetes mellitus, lung diseases, obesity, immune-compromised state and kidney diseases predominantly affecting and leads to rise in mortality. Environmental contamination via contaminated surfaces in areas with high infective cases like quarantine centers or hospitals are also an important aspect of spreading the virus. So, routine cleaning with sodium dichloroisocyanurate disinfectant is needed. Protective antibodies against SARSCoV2 receptors binding domain of spike protein and nucleocapsid protein appears on day 14 following symptom onset. The antibody titers by Enzyme linked Immunosorbent assay (ELISA) correlates with neutralizing activity and protective nature of antibody. To understand the risk of reinfection, serological screening tool will be an important tool for population immunity or people already infected. SARS CoV 2 and SARS CoV share similar spike protein gene and RBD, i.e. capability of viral transmission in humans. Whole genome sequencing of SARS CoV 2 is similar to SARS like bat CoVs. Symptoms may appear 2-14 days after exposure to the virus. Most common and severe manifestation is pneumonia which presents with fever, cough, dyspnea and bilateral lung infiltrates on chest imaging. Specimen is collected from upper respiratory tract (nasopharynx and/or oropharynx) and lower respiratory tract (such as sputum, Broncho Alveolar Lavage (BAL)). The diagnosis can be made via RT-PCR, Rapid antigen test, Rapid antibody test etc. but disease progression can be seen via radiological test like chest X-ray and CT. The mainstay of therapy of COVID-19 is supportive and preventive requiring quarantine and waiting self-recovery.

**Keywords:** COVID-19, SARS CoV 2, Pandemic, Environmental contamination, Quarantine, Sodium Dichloroisocyanurate, RT-PCR.

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## INTRODUCTION

Coronaviruses are the most newly emerging zoonotic virus which is transmitted between animals and humans. [1] Previously, known effects of coronaviruses are common cold, severe acute respiratory syndrome (SARS) and middle-east respiratory syndrome (MERS). [2] Many more coronaviruses still present in environment which are not found in humans till now [3-5].

Coronavirus disease is caused by coronaviruses which first discovered from Wuhan, China in Dec 2019 [6]. This virus was not previously identified in humans. On 12<sup>th</sup> January 2020, World Health Organization (WHO) renamed it as 2019-novel coronavirus (2019-nCoV) and subsequently, on 11<sup>th</sup>

February 2020, International committee on Taxonomy of Viruses of WHO coronavirus study group, named SARS CoV 2 and disease called COVID-19 [7-9].

In the end of year 2019, many cases which were identified as pneumonia Wuhan. Later, it was discovered that the pneumonia caused by a new strain of virus SARS-CoV2. Due to rapid increase in cases in a very short period of time, on 30<sup>th</sup> January 2020, outbreak was declared by Public Health Emergency of International Concern (PHEIC) and global pandemic declared by the WHO [10]. At that time, epicenter of pandemic was Wuhan which later changed to Europe and USA [11, 12]. In the beginning of outbreak, studies in Wuhan's seafood market which sold alive animals for food purposes, showed initial association of

infection to people working or visited the market. Later, the market was closed for disinfection purpose [13]. Now, as outbreak is progressing, person to person transmission became primary source. Due to animal spread of virus, it was necessary to find the infection in domestic animals transmitting to humans. Studies showed absence of any evidence of infectivity with pets. However, an experimental study showed viral multiplication in cats if intranasal inoculated. But Center for Disease Control (CDC) recommends that pets should be kept away from other animals or people outside the household.

### Mode of transmission and infectivity period of disease

Dominant way of transmission is respiratory droplets released via cough, sneeze, talks etc. Infection occurs due to inhalation or touching the contaminated surfaces with droplets and then touches own mouth, nose and eye [14, 15]. The aerosol spread is uncommon but a report revealed virus remains in aerosols for about three hours in experimental conditions [14]. The incubation period is 2 weeks after exposure, major occurs within 4-5 days as viral RNA peaks during this period. Virus is also likely to spread via non-respiratory methods like stool, blood and ocular secretions but no such study has substantial evidence to prove transmission [16, 17]. All ages and both sexes are equally affected. Middle aged and elders >70 years age or people with co-morbid conditions like Diabetes mellitus, chronic liver disease, lung disease, cardiovascular disease, obesity, immune-compromised state and kidney disease predominantly affecting and leads to rise in mortality [18-20].

Infectivity period is uncertain in COVID-19. Virus RNA from upper respiratory samples after symptoms onset is usually higher than later phases of disease [15, 21, 22]. So, the patient might be more infectious during earlier infection stage. If a viral RNA is detected in upper respiratory tract sample, that doesn't imply presence of infectious virus always. A study from China revealed infectiousness of virus starts 2-3 days before onset of symptoms and peaks in 7 hours and decline in 7 days, particularly after isolation [15]. However, patients without any symptoms can transmit the disease. In mild disease, most patients show negative tests in 10 days but in severe cases, patient shows longer duration of infectivity. So, if the patient's upper respiratory sample contain viral RNA, that doesn't correlate with infectivity of virus. According to a study, virus was not detected in respiratory sample when viral RNA level was < 10<sup>6</sup> copies/ml [22].

Environmental contamination is also an important way of spreading the virus. Contaminated surfaces contain viruses in areas with high infective cases like quarantine centers or hospitals [14]. So, routine cleaning with sodium dichloroisocyanurate disinfectant is needed. Various disinfectants like ethanol

at concentration between 62-71% inactivates virus in one minute [24]. However, viral persistence on surface depends on type of surface, ambient temperature, relative humidity and size of initial inoculum [25, 26].

### Immunity and reinfection

Studies revealed presence of protective antibodies against receptors binding domain of spike protein and nucleocapsid protein appears on day 14 following symptoms onset. The antibody titers by Enzyme linked Immunosorbent assay (ELISA) correlates with neutralizing activity of antibodies that states protective nature of antibody [22]. The US-FDA authorized tests that qualitatively identifies antibody against SARS-CoV 2 in blood [27]. To understand the reinfection risk, serological screening can be an important investigation for population immunity or people already infected.

### Coronavirus structure and genome

SARS-CoV 2 is a  $\beta$ -coronavirus which is enveloped non-segmented positive sense single stranded RNA virus. It belongs to subfamily Orthocoronaviridae and family Coronaviridae [11, 54]. The genera are as alpha ( $\alpha$ ), beta ( $\beta$ ), gamma ( $\gamma$ ) and delta ( $\delta$ ). Alpha ( $\alpha$ ) and beta ( $\beta$ ) infect animals and gamma ( $\gamma$ ) and delta ( $\delta$ ) infect birds. There are six coronaviruses which infect humans in  $\alpha$  CoV is HCoV229E & HCoVNL63 and  $\beta$  CoV is HCoV-HKU1, HCoV-OC43, SARS-CoV and MERS CoV. Coronavirus structure is round or elliptical, often pleomorphic with diameter 60-140 nm. Two third of viral RNA is located in first open reading frame (ORF 1a/b) and encodes for 16 non-structural proteins (NSP). Remaining one third of viral RNA encodes essential structural proteins like spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, nucleocapsid (N) protein and accessory proteins which interfere with host immune system [29, 30].

SARS CoV 2 and SARS CoV share similar spike protein gene and RBD, i.e. capability of viral transmission in humans [31]. Whole genome sequencing of SARS CoV 2 is similar to SARS like bat CoVs. Chan et al. proven that genome of new CoV isolated from cluster patients with atypical pneumonia showed 89% nucleotides similar to bats SARS CoV like CoV2XC21 and 82% similar with human SARS CoV [4]. That's why new virus called SARS CoV 2 and bats are suspected as natural host of virus origin. Another study revealed mutation in non-structural proteins of COVID-19 which is playing a role in its infectious capability and differentiation mechanism. So, there is need of regular monitoring of current CoV for their virulence and epidemic spread.

### Clinical manifestations

Like any other viral infection, COVID-19 also presents with similar complains. Symptoms may appear 2-14 days after exposure to the virus. Most common and severe manifestation is pneumonia which presents with fever, cough, dyspnea and bilateral lung infiltrates

on chest imaging. Worldwide, there are several other symptoms presented by COVID-19 positive patients like fatigue, dry cough, anorexia, myalgia, sputum production, diarrhea, nausea and vomiting etc. [19, 39].

The CDC prepared a check list for symptoms presented by COVID-19 affected patients are fever or chills with/without rigor, cough, dyspnea, fatigue, body ache, headache, new taste loss or smell, sore throat, congestion, runny nose, nausea, vomiting, diarrhea. The warning signs which may require emergency care or hospitalization are trouble breathing, pressure in the chest or pain, inability to wake or stay awake, new confusion [40, 41].

## DIAGNOSTIC METHODS

### Collection, handling and storage

Sample collection and storage is challenging for diagnosis of COVID-19. The WHO recommends specimen collection from upper respiratory tract (nasopharynx and/or oropharynx) and lower respiratory tract (such as sputum, Broncho Alveolar Lavage (BAL) or endotracheal aspirate). BAL collected only in patients on mechanical ventilation. Lower respiratory tract samples are stored at 4°C [42].

### RT-PCR

Reverse transcriptase polymerase chain reaction (RT-PCR) is used for amplification of genetic material collected from specimen. It involves synthesis of double stranded DNA from RNA of virus. The whole procedure involves three steps; lysis, extraction and PCR. Lysis buffer is used to get a lysate from the specimens and then the nucleic acids are to be recovered using automated extraction system, and also by manual extraction following manufacturer's instruction. RT-PCR should be performed on the extraction eluter of specimens. Pooling can also be employed at where samples are collected in big amount. Two stage approaches is followed and then any positive pools are tested later to determine which individual is positive. This approach can save reagents and also reduces the turnaround time. The CDC recommends identifying the presence of nucleic acid targets specific to SARS CoV 2. The test is based on the initial genetic sequence released by Shanghai public health clinical center and school of public health, Fudan University, Shanghai, China [43].

The US CDC have developed a kit containing PCR primer probe sets for two regions of viral nucleocapsid gene (N1 and N2) and for humans RNase P gene to ensure successful RNA extraction. The WHO primer probe sets target the SARS CoV 2 RNA dependent RNA polymerase and envelope (E) genes [44]. These tests use cycle threshold (CT) of < 40 to be positive. Both above tests are highly sensitive and specific with minimal cross reactivity with other coronavirus strains.

If a patient showed a positive test result, then at least two upper respiratory tract samples collected in 24 hour interval to be negative to document SARS CoV 2 clearance before release from observation [45]. Many new tests have been introduced for COVID-19 but their diagnostic accuracy is questionable because of lack of incomplete understanding of virus, different methods of collecting and preparing the samples and absence of standard test.

### Viral culture

Viral culture using Vero-CCL-81 cells is possible but not commonly used because of low sensitivity and long turnaround time for virus detection [46].

### Rapid antigen detection test

RDT detects presence of SARS CoV 2 antigen from samples which bind to specific antibodies fixed to a paper strip. Samples are taken from nasopharyngeal / nasal swab which is directly placed into extraction buffer or reagent. The test shows visually detectable signals usually in 30 minutes. The test limitation is only when virus is actively replicating, test result varies with illness onset, concentration and quality of specimen, reagents in test kit [47, 48]. False positive result due to antibodies on stripe recognizes antigens of virus other than SARS CoV 2 like SARS CoV. Monoclonal antibody against nucleocapsid protein of SARS CoV 2 has been developed [49]. The advantages of the test are inexpensive, can be used bedside and for surveillance of testing. Its results are more sensitive and specific when done early in infection, when viral load is highest.

### Rapid antibody diagnostic test

The basis of test is the detection of IgM and IgG antibodies. [50-53] The ELISA or rapid card test can be used to detect antibodies. IgG antibodies appear after two weeks of symptom onset or with recovery, i.e. its use is limited in management and transmission prevention of SARS CoV 2. The negative test doesn't exclude recent infection. However, it can be used with RT-PCR for antibody response. This test may not be used to diagnose an active infection. In general, a positive antibody test is presumed to mean a person has been infected with SARS CoV 2 but doesn't clarify presence of ongoing infection. It is hard to define immunity from reinfection if they have antibody against viral components.

### Radiological tests

Plain chest x-ray is an early and easy supportive test for management. Chest X-ray shows bilateral pulmonary infiltrates.

Computed tomography (CT) of chest is more sensitive than plain chest x-ray. Most CT finding shows predominant peripheral, bilateral, lower lobes involvement with ground glass opacities or mixed ground glass opacity and consolidation, vascular involvement, traction bronchiectasis. The limitation is

presence of any co-infection or alternative diagnosis [54].

### Laboratory tests

COVID-19 infected patient shows decreased albumin, elevated C-reactive protein, elevated lactate dehydrogenase level and lymphopenia [55]. In severe cases with multi organ involvement, patients show elevated erythrocyte sedimentation rates, elevated aspartate aminotransferase, elevated alanine aminotransferase, elevated creatinine kinase level, leukopenia, leukocytosis increased bilirubin and creatinine levels [18, 19].

### Management [56]

#### Management of mild cases

Patients complain of fever or upper respiratory infections are isolated. Patients with these symptoms can present to primary care centers, outpatient department (OPD) or community outreach activities. These patients can be treated at Covid Centres or home isolation. Patient's detailed clinical history with co-morbidities taken and counsel about warning signs. If a patient have co-morbidities then closely monitored and in emergency, immediately shifted to Covid care center or Covid hospital.

In mild cases, patients are followed up daily for temperature, vitals and oxygen saturation (SpO<sub>2</sub>) monitoring. They can be treated symptomatically with antipyretics, adequate hydration and nutrition.

#### Management of moderate cases

Patients complain of fever, cough, and dyspnea (likely has pneumonia) or have > 24 breaths per minute respiratory rate and oxygen saturation (SpO<sub>2</sub>) < 94%; is been isolated in Covid care center or Covid hospital. The detailed clinical history with co-morbidities, vital signs monitoring, SpO<sub>2</sub>, chest x-ray and other indicated investigations are done. In moderate cases, treatment done with oxygen support (target SpO<sub>2</sub> is 92 – 96% and 88-92% in COPD patients). If HFNC or simple nasal cannula used, then N95 mask should be applied with it. Awake proning used as a rescue therapy. Patients daily monitored with 12 lead ECG, complete blood count with differentials, Absolute lymphocyte count, renal function tests and liver function tests with follow up C-reactive protein, D-dimer and ferritin every 48 hours. Tab Hydroxychloroquine 400mg BD first day followed by 200mg BD for 4 days (after ECG Assessment). Consider IV methylprednisolone 0.5 to 1 mg/kg 3 days (within 2 days of admission or if oxygen requirement is increasing and if inflammatory markers increased). Anticoagulants are given prophylactically unfractionated heparin (UFH) or low molecular weight heparin (LMWH) (Enoxaparin 40 mg per day SC). Close monitoring of patients is required for disease progression.

#### Management of severe cases

Patients complain of severe respiratory distress requiring mechanical ventilation or > 30 breaths per minute and SpO<sub>2</sub> < 90%; are isolated and given supplemental oxygen therapy immediately. Initially oxygen therapy at 5 L/min and titrate the flow at a rate to achieve SpO<sub>2</sub> ≥ 90%. Children with warning signs receive oxygen therapy during resuscitation to reach SpO<sub>2</sub> ≥ 94%.

Currently, there are several therapies under trial given to specific patients only. Remdesivir is an investigational nucleotide analog with broad spectrum antiviral activity. The drug dose is 200 mg IV followed by 100 mg IV daily 5 days. The drug is contraindicated in patients with AST/ALT > 5 times, renal impairment (i.e. GFR < 30ml/min/m<sup>2</sup> or hemodialysis), pregnant, lactating females and children < 12 years of age.

Convalescent plasma can be used in patients with moderate disease who are not showing signs of improvement. Precautions include ABO compatibility, cross matching of the donor plasma and neutralizing titer of donor plasma. Post transfusion monitoring of patients done for transfusion related adverse reactions and avoid if IgA deficiency or immunoglobulin allergy. The dose can be 4-13 ml/kg or 200 ml single dose over more than 2 hours.

Tocilizumab can be used with moderate disease with progressively increasing oxygen requirements and in mechanically ventilated patients not showing signs of improvement. The prerequisites include raised inflammatory markers (e.g. CRP, Ferritin, IL-6), secondary infections and neutropenia, active infections and Tuberculosis should be ruled out. The dose can be 8 mg/kg (maximum 800 mg at one time) given slowly in 100 ml Normal Saline over 1 hour (can be repeated once after 12 to 24 hours if needed).

## SUMMARY AND CONCLUSION

COVID-19 is caused by β-coronavirus (SARS CoV 2), discovered in Wuhan (seafood market), China in 2019 and declared pandemic on 30<sup>th</sup> Jan 2020 by the WHO. The transmission via respiratory droplets like sneeze, coughing etc. is primary source. The incubation period is 2 weeks after exposure. Middle aged and elders >70 years age or people with co-morbidity predominantly affected and leads to rise in mortality. Environmental contamination via contaminated surfaces in areas with high infective cases like quarantine centers or hospitals are also an important cause of virus transmission. So, routine cleaning with sodium dichloroisocyanurate disinfectant is needed. Protective antibodies against SARS CoV 2 receptors binding domain appear on day 14 after symptom onset. The antibody titers can correlate with neutralizing and protective activity of antibody. To estimate the reinfection risk, serological screening tool can be used as an important investigation for immunity or people already infected. SARS CoV 2 and SARS CoV share

similar spike protein gene and RBD, i.e. capability of viral transmission in humans. Whole genome sequencing is similar to SARS like bat CoVs. Symptoms may appear 2-14 days after exposure. Most common and severe manifestation is pneumonia which presents with fever, cough, dyspnea and bilateral lung infiltrates on chest imaging. Specimen is collected from upper respiratory tract (nasopharynx and/or oropharynx) and lower respiratory tract (such as sputum, Broncho Alveolar Lavage (BAL) or endotracheal aspirate). The diagnosis can be made via RT-PCR, Rapid antigen test, Rapid antibody test etc. but disease progression can be seen via radiological tests. The mainstay of management is quarantine and symptomatic treatment.

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