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## **Corona Virus Disease-2019 (Covid-19): An Insight Into The Pandemic**

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### **Abstract:**

The new Covid-19 viral infection outbreak occurred in the last half of December 2019 in the Wuhan city of China, and has jeopardized the functioning of the whole world for past several months. The disease was officially named as Corona Virus Disease-2019 (Covid-19) by World Health Organisation (WHO) on February 11, 2020, and was declared a pandemic. Human transmission is via droplet as well as aerosols. Elderly individuals and those with comorbidities are at a higher risk of developing complications. As of now there is no definitive treatment for the infection, and the research on vaccine is progressing rapidly. Till then stringent infection control practices are advised worldwide in order to prevent spread of the infection.

**Keywords:** Corona virus, Covid-19, SARS-CoV2, pandemic

### **Introduction**

Corona viruses are a large family of viruses causing a broad spectrum of infections ranging from common cold to severe major diseases such as the Severe Acute Respiratory Distress syndrome (SARS) in China in 2003 and the Middle East Respiratory Syndrome (MERS) in Saudi Arabia in 2012. The SARS and MERS infections have spread to several countries causing high mortality and morbidity [1]. The latest Covid-19 outbreak came to light when China informed the WHO of a cluster of pneumonia cases of an unknown aetiology in the Wuhan city of Hubei province on December 31, 2019. The WHO later issued a statement saying Chinese researchers have decided the causative agent as a novel Corona Virus [2]. A large proportion of Covid-19 infections were undocumented prior to the implementation of travel restrictions and other control measures in China on January 23, 2020. These undocumented infections, where many of them were only mildly symptomatic, have facilitated the rapid spread of the virus throughout the China. According to Dr. Jeffrey Shaman, professor Environmental Health Sciences (in the International Research Institute for Climate and Society/Earth Institute) and director of Climate and Health Program, the explosion of Covid-19 cases in China was largely driven by asymptomatic individuals and those with mild, limited symptoms [3]. As per WHO statistics, till September 20, 2020, the

Covid-19 infection has spread across 215 countries/regions, infecting about 30.1 million people with around 959,000 demises throughout the world. About 21.1 million cases recovered from the infection.

### Virological charecteristics

The Alpha and Beta Corona viruses are known to infect human beings [4]. The Covid-19 virus is genetically more similar to SARS-CoV than to MERS-CoV, and hence the name SARS-CoV2. Though the human angiotensin-converting enzyme 2 receptor (ACE-2 receptor) is the same for both SARS-CoV1 and SARS-CoV2, the S protein of SARS-CoV2 binds more weakly to human ACE 2 receptor, resulting in less severe infection in patients infected by SARS-CoV2 compared to SARS-CoV1 [5].



**Figure 1:** SARS-CoV structure. 1. Envelope 2. RNA 3. Nucleo capsid nucleoprotein 4. Spike glycoprotein 5. Hemagglutinin-acetyl esterase glycoprotein 6. Small envelope glycoprotein 7. Membrane glycoprotein

### Immune response to Corona Virus

Both the innate and acquired immune responses are activated by SARS-CoV2. T lymphocytes and dendritic cells are activated through pattern recognition receptors (PRRs) including C-type lectin-like receptors, Toll-like receptor (TLR), NOD-like receptor (NLR), and RIG-1-like receptor. CD4<sup>+</sup> T cells stimulate B cells to produce antibodies including IgG and IgM, whereas CD8<sup>+</sup> T cells can directly kill virus infected cells. T helper cells produce pro-inflammatory cytokines and mediators to help the other immune cells. However SARS-CoV2 suppresses T cell function by inducing programmed cell death. Humoral immunity including complement factors such as C3a and C5a and specific B cell derived antibodies are also essential in combating SARS-CoV2 infection. The envelope spike(s) glycoprotein of SARS-CoV binds to ACE 2 receptor, and then membrane fusion occurs [6]. After entering the target cell, viral RNA is encapsulated, polyadenylated, and encodes various structural and non-structural polypeptide genes. These polypeptides are cleaved by proteases that exhibit chymotrypsin like activity [7]. The virus induces the expression of numerous inflammatory

factors, maturation of dendritic cells and the synthesis of Type I interferons (IFNs) which limits the viral spread and accelerates phagocytosis of viral antigens resulting in clinical recovery [8]. However, the N protein of virus helps to escape from the immune response and overreaction of the immune system is responsible for the generation of very high levels of inflammatory mediators and free radicals [9]. These induce local damage to the lungs and the other organs, and the overspill results in multi organ failure and even death in the worst cases [10].

### **Origin and intermediate host**

In Covid-19 pandemic, Malayan pangolins, an ant eating mammal often used in Chinese traditional medicine may be the potential intermediate host based on the 99% genetic homology of Corona virus detected in Pangolins with SARS-CoV2. However, this may require further confirmation [11].

### **Symptoms**

Fever, as an initial symptom of Covid-19 infection, was present in 98% patients, and may be accompanied by dry cough, myalgia, headache, sore throat, rhinorrhoea, chest pain, nausea and vomiting. Some patients developed acute respiratory distress syndrome (ARDS) within two days. Breathlessness was noted about 1 week after the onset of the disease and was present in 55% of patients [12]. In severe cases patients quickly progressed to develop ARDS, septic shock, metabolic acidosis and coagulopathy, hence it is prudent to screen patients presenting with fever and/or respiratory symptoms without pulmonary imaging abnormalities for Covid-19 virus for an early diagnosis [13].

Human to human transmission occurs among close contacts (about 6 feet) mainly via respiratory droplets through contact with mucous membrane of the mouth, nose and possibly eyes. There is also evidence for hospital based transmission among patients and Health care workers. A family cluster caused by transmission from an asymptomatic individual was also documented [14].

Common clinical features in the early stage are [15]:

- \*Fever (80-90%)
- \*Fatigue (38-70%)
- \*Dry cough (59-68%)
- \*Anorexia (40%)
- \*Myalgia (15-35%)
- \*Dyspnoea (19-31%)
- \*Sputum production (27-34%)

Less common symptoms are:

- \*Headache
- \*Sore throat\ Rhinorrhoea
- \*Gastrointestinal symptoms (nausea and diarrhoea)
- \*Loss of taste and smell

### Complications [16]

1. ARDS (17-29%)
2. Arrhythmias (44%)
3. Acute cardiac injury (22-31%)
4. Shock (20-23%)
5. Acute kidney injury (8-23%)
6. Secondary infection (31%)
7. Myocarditis / Cardiomyopathy (33%)

Few patients with Covid-19 infections had prominent upper respiratory tract signs (rhinorrhoea, sneezing and sore throat) when compared to SARS and MERS, indicating that the target cells might be located in the lower respiratory tract. The incubation period of SARS-CoV2 ranges from 7-14 days which is more than SARS-CoV (4-7 days) and MERS-CoV (5 to 7 days). ARDS usually occur in the 2nd week (8-9 days), hence requiring a longer period of observation for patients with Covid 19 infection.

In studies by Chen et al and Wang et al, the major complications included ARDS in hospitalised patients (31-55%), acute cardiac injury (7-12%), cardiac arrhythmia (16%), acute kidney injury (3-7%) and shock (4-9%). Many severe cases required non-invasive (10-24%) ventilation and invasive mechanical ventilation (4-12%). Most of the clinical worsening and complications developed from second week onwards, coinciding with the peak replication of the virus. Extracorporeal membrane oxygenation (ECMO) was required in 3-5% patients due to persistent hypoxemia. SARS-CoV2 has a higher ability to spread than MERS-CoV and SARS-CoV, but it is less lethal [13,17].

### Diagnosis

Patient's travel and contact history with an infected person is very important, especially 2 weeks prior to the onset of symptoms. Asymptomatic or pre-symptomatic patients can spread the virus to people in a gathering or in a family. The people who are discharged from the hospital must be quarantined for an additional 14 days to prevent further transmission, as some patients may show persistent viremia but may not indicate infectivity [18].

### Laboratory investigations

Complete blood count, coagulation profile, renal and liver function tests, creatine kinase, lactate dehydrogenase and serum electrolytes were done at the time of admission. Respiratory specimens including nasal and pharyngeal swabs, bronchoalveolar lavage fluid, sputum and bronchial aspirates were also tested for common viruses including influenza, Avian influenza, Respiratory Syncytial virus, Adenovirus, Para influenza virus, SARS-CoV and MERS-CoV using real time polymerase chain reaction assays. Routine bacterial and fungal cultures were also done.

Routine blood results on admission showed leucopenia (25%) and lymphopenia (63%). D-Dimer and prothrombin time were higher in ICU patients when compared to non ICU patients. Similarly, aspartate aminotransferase, C-reactive protein, ferritin and high-sensitivity cardiac troponin I were elevated in ICU patients. An increase in renal parameters, creatine kinase and lactate dehydrogenase were observed in seriously ill patients, indicative of multi organ dysfunction syndrome. Serum albumin and haemoglobin were reduced. Elevated procalcitonins levels were seen in those with secondary bacterial infection. Most of the results are indicative of the presence of cellular immune deficiency, coagulation

activation and multi organ dysfunction resulting in fatal outcome [13].

### **Radiological features**

Chest X-ray chest can be normal in one third of patients during the initial phase and are not specific for the infection, and could overlap with other infections. There are also recommendations regarding the performance of the X-ray chest x-ray or computed tomography (CT) thorax, as it is better to avoid movement of the patient in the hospital for preventing the spread. The most common findings include lobar or multi lobar bilateral lung consolidation, predominantly involving the lower and peripheral areas of the lobes.

#### ***CT thorax***

1. Early stage (0-4 days after the onset of symptoms) - Ground glass opacities with subpleural distribution involving predominantly the lower lobes. Some patients may have normal CT. In a study of 21 patients with SARS Cov-2 infection, 14% had normal CT chest at the time of diagnosis.
2. Progressive stage (5-8 days after the onset of symptoms) - The findings evolve to rapid involvement of two lungs or multi lobar distribution with ground glass opacity, crazy paving and consolidation of air spaces [22].
3. Peak stage (9-13 days after the onset of symptoms) - The consolidation becomes denser and it was present in almost all the cases. Besides there will be residual parenchymal bands also.
4. Absorption phase (more than 14 days after the onset of symptoms) - No crazy paving pattern was observed. Ground glass opacity can persist [19].

### **Histopathology**

The autopsy and pathological analysis of a patient who died of SARS-CoV2 was consistent with the pathology of viral infection and ARDS, and was similar to that of SARS and MERS. Pathological findings included desquamation of pneumocytes, hyaline membrane formation, interstitial lymphocyte infiltration with presence of multinucleated syncytial cells in both lungs [20].

### **Cytokine release Syndrome in severe Covid-19 infection**

SARS-CoV2 infection results in monocyte, macrophage and dendritic cell activation. Release of interleukin-6 (IL-6) then instigates an amplification cascade resulting in increased cytokine production systemically. This contributes to the pathophysiology of severe Covid-19 infection with ARDS, which may be treated with IL-6 antagonist like tocilizumab, sarilumab and siltuximab.

### ***Mechanism***

SARS-CoV2 infects the alveolar epithelial cells, mainly type 2 cells, through ACE-2 receptor. The destruction of epithelial cells and the increased cell permeability leads to the release of the virus. The SARS-CoV2 activate the innate immune system, macrophages and other innate immune cells [23], also release a large number of cytokines and chemokines including IL-6, besides capturing the virus. Adaptive immunity is also activated by antigen

presenting cells (dendritic cells). T cells and B cells also promote the secretion of inflammatory cytokines. Besides their antiviral role, pro-inflammatory cytokines increases the vascular permeability and inflammatory exudate in the alveoli resulting in ARDS and respiratory failure [21].

Severe Covid-19 criteria require one of the following:

1. Respiratory rate >30/min
2. Oxygen saturation <93% while resting
3. PaO<sub>2</sub>/FiO<sub>2</sub><300 mm Hg

Critical Covid-19 criteria require one of the following:

1. Respiratory failure requiring mechanical ventilation
2. Shock
3. Admission to ICU with other organ failure

### **SARS-CoV2 Laboratory diagnosis**

All suspected cases as per case definition should undergo necessary laboratory diagnosis for confirmation of infection as per WHO and MoHFW guidelines.

1. Respiratory material (nasopharyngeal and oropharyngeal swab in ambulatory patients and sputum and/or endotracheal aspirate or bronchoalveolar lavage with severe respiratory disease). It should be sent in viral transport media with cold chain maintained.
2. Serum for antibody testing - Acute and convalescent samples may be sent. Nucleic acid amplification test /RT PCR are currently used for SARS-CoV2 infection [22].

Covid -19 testing positivity rate [23]:

<b>Types of specimen</b>	<b>Positive</b>
Bronchoalveolar lavage fluid	93%
Bronchoscopic brush biopsy	46%
Sputum	72%
Nasopharyngeal swab	32%
Feces	29%
Blood	1%
Urine	0.1%

**PCR test***Advantages:*

- \*Highly specific (100% specificity)
- \*Tests become positive in the early phase of disease

*Disadvantages:*

- \*RT-PCR is complicated and expensive and mainly suited to centralized reference laboratories.
- \*Takes 4-6 hours
- \*PCR becomes negative in the later phase of the disease as the patient's immunity build up.

**Antibody test - Enzyme linked immuno sorbent assay (ELISA)**

- \*IgM antibody rises first after infection. It is indicative of active infection.
- \*IgG type antibody rises later and it is an indication of past infection.

*Advantages:*

Used for the rapid screening of SARS-CoV2 carriers, symptomatic or asymptomatic, in hospitals, clinics and test laboratories. Covid-19 rapid test detects IgG and IgM antibodies to Covid-19 in whole blood, serum and plasma samples. IgM-IgG combined assay has better utility and sensitivity compared with a single IgG or IgM test alone. Antibody tests are cheaper and results are faster.

*Disadvantages:*

- \*Negative in the early phase of the disease. IgM titres starts to rise only 3-7 days after the onset of symptoms.
- \*Specificity of the test is less than RT-PCR, especially when it is used primarily as a standard diagnostic test.

**Laboratory parameters for severe illness:**

1. D-dimer > 1000 ng/ml
2. CPK twice the upper limit of normal
3. CRP > 100 mg/L
4. LDH > 245 U/L
5. Elevated Troponin level
6. Absolute lymphocyte on admission < 0.8 x 10<sup>9</sup>/L
7. Ferritin > 300 ng/ml

**Risk factors for severe disease [12]**

- \*Male sex and older age (> 64 years) - ARDS is common.

\*Any one of the following condition:

- Cardiovascular disease (10.5%)
- Diabetes mellitus (7.3%)
- Chronic respiratory disease (6%)
- Hypertension (6%)
- Cancer (6%)
- Chronic Kidney Disease (6%)
- Prior stroke (4%)

## **Management**

SARS-CoV2 presents as mild disease in 81% of patients, severe disease in 14% and critical disease in 5% of patients. Patients with mild disease usually don't require admission. Among hospitalized patients, 10-20 % are admitted to ICU, 3-10 % require intubation and 2- 5% dies.

Treating Physicians can only provide supportive care to COVID- 19 patients. Previous experience with treatment for SARS and MERS has led physicians in China, other South East Asian countries and European nations to use multiple therapies to prevent viral multiplication inside the human cells. These included antiviral agents, immunosuppressants, steroids, convalescent plasma, management of sepsis and other complications besides respiratory support.

## ***Supportive care***

These include oxygen therapy, conservative fluids supply, managing complications according to what each patient develops, empirical antimicrobial drugs, antipyretic/analgesics, mechanical ventilation and corticosteroids if indicated.

Endothelial infection and immune mediated endothelitis were demonstrated in blood vessels on autopsy of Covid-19 patients. Vascular endothelium has got active paracrine, endocrine and autocrine functions which are required for the maintenance of vascular homeostasis. Histologically, there are viral elements and accumulation of inflammatory cells with evidence of endothelial and inflammatory cell death. Endothelial dysfunction leads to micro vascular dysfunction in multiple organs which includes heart, blood vessels, lung, kidney and intestine through the presence of ACE-2 receptors. In the heart, there was histological evidence of myocardial infarction, but no sign of lymphocytic myocarditis [24].

Respiratory dysfunction and failure are the major cause of death. Hence, respiratory support in the form of general oxygen therapy, high flow oxygen, non-invasive ventilation and invasive mechanical ventilation are necessary to save the lives of these patients. Patients with severe, respiratory symptoms may require ECMO. Management of sepsis due to bacterial or fungal infection should be carried out as per sepsis protocol, along with support to other vital organs in case of complications like myocardial infarction, stroke, hepatic and renal failure. Similarly, conservative fluid management, maintenance of electrolyte balance, correction of anaemia and prophylaxis against deep vein thrombosis are essential [25].

## ***Role of Chloroquine or Hydroxychloroquine (HCQ)***

Chloroquine / HCQ inhibit viral cell entry and endocytosis. It's a widely known, easily available and affordable antimalarial agent for both treatment and prophylaxis for Covid-19



infection. The SARS-CoV2 is known to bind to human cells via the ACE-2 receptor. Chloroquine, in in-vitro studies, has shown to affect the glycosylation process of ACE-2 receptor, thus causing the Vero cells pre-treated with chloroquine to become refractory to SARS-CoV infection. HCQ has the same mechanism of action with a better safety profile and is a preferred prophylactic medication. Both these drugs have also shown to have immune-modulatory effects and can suppress the release of inflammatory cytokines like IL-6 and IL-10. This effect can help in mitigating the cytokine storm in critically ill SARS-CoV2 patients if started early in the course of the disease. The suggested dose for HCQ is 400 mg twice daily on day 1, followed by 200 mg twice daily for 4 days. HCQ has a superior in-vitro antiviral effect when compared to chloroquine [26].

### ***Antiviral therapy***

Antiviral therapy mainly aims at reducing the viral load. Antivirals can be initiated on a compassionate basis and whatever treatment strategy is there, it has to be started before clinical deterioration. No proven benefits have been observed so far, except for stray reports of success. The options available are a combination of lopinavir/ritonavir, ribavirin without any randomized control trial. Many of these antiviral agents are undergoing evaluation in clinical trials, but none have yet shown to be clearly effective, and many can be reasonably expected to cause toxicity.

\*Remdesivir, a nucleotide analogue, was used in the treatment of diseases caused by Ebola and Marburg viruses, and in SARS and MERS virus infection. It is a broad spectrum antiviral acting against polymerase enzyme of the virus [27].

\*Favipiravir is an agent which can be considered in moderate-severe infection. Its mechanism of action is similar to remdesivir. In 2014, it was approved for the treatment of influenza in Japan. In the tissue the molecule undergoes phosphoribosylation to favipiravir-RTP which acts as a substrate for RNA polymerase (RdRp) enzyme, which is mistaken by the enzyme as a purine nucleotide, resulting in inhibition of its activity leading to the termination of viral protein synthesis. The dose schedule is 1800 mg twice daily on day 1, followed by 800 mg twice daily for 7 days, up to a maximum of 14 days. The side effect profile is acceptable with asymptomatic hyperuricemia and mild elevation in transaminases. However, the drug has teratogenicity and must never be used in pregnant women [28,29].

\*Antivirals like lopinavir, draunavir, remdesivir, ribavirin inhibit RNA translation process.

\*Arbidol inhibits membrane fusion of the viral envelope.

\*Camostatmesylate inhibits viral cell entry [25]

### ***Cytokine storm or Cytokine release syndrome***

It is a form of systemic inflammatory response characterized by the release of a series of pro-inflammatory cytokines, as in sepsis. These cytokines include TNF- $\alpha$ , IFN- $\alpha$ , IL-1 $\beta$ , IFN $\beta$ , IL-2, IL-6, IFN $\gamma$  and MCP-1. These cytokines induce immune cells to release free radicals which results in ARDS and multi-organ dysfunction syndrome. It is seen in critically ill patients and may benefit from immunosuppressive therapy. There is a chance for developing secondary bacterial or fungal infection following this treatment. Tocilizumab, an IL-6 blocking monoclonal antibody, along with steroids have been used to treat cytokine storm [21]. The WHO has advised against routine use of steroids in SARS-CoV2 associated pneumonia or ARDS, and its use should be judicious in critically ill patients at lowest dose for the shortest possible time [30].

### ***Convalescent Plasma and antibody generation***

Convalescent plasma (CP) therapy has been applied in the prevention and treatment of several infectious diseases for more than one century. It is a classic adaptive immunotherapy. CP therapy was successfully used in the treatment of SARS, MERS and 2009 H1N1 pandemics with satisfactory safety and efficacy. However, it was not found to be useful in Ebola virus infection.

The plasma must be taken from recently recovered Covid-19 patients with neutralizing antibody titre > 1:640. The neutralizing antibody titre in the recipient must exceed 1:80 to achieve effective CP therapy. CP must be given within 16.5 days from onset of the illness, preferably before 14 days. No significant adverse reaction was noted. At a dose of 1200 ml, CP was well tolerated and could significantly increase or maintain the neutralizing antibodies at a high level leading to disappearance of viremia within 7 days. Radiological improvement was also seen within 7 days. Hence, it can be taken up as a rescue therapy in Covid-19 infection.

### ***Dexamethasone***

The RECOVERY trial tested the use dexamethasone in Covid-19 patients. At a dose of 6 mg per day, dexamethasone was found to be effective in reducing the death rate by one third in ventilated patients and by one fifth in patients receiving oxygen alone. Dexamethasone is believed to be the first drug to have mortality benefit in Covid-19 infection [31].

### ***Doxycycline and Ivermectin***

The outcome of clinical trials using the combination of doxycycline and ivermectin, along with zinc and vitamin D3 may be helpful in the prevention and treatment of Covid-19 is to be published.

### **Prevention & Public health measures**

Isolation i.e. home voluntary quarantine, social distancing of population at risk especially those above the age of 60 years and those with co-morbidities are absolutely essential to prevent community spread. Closure of schools, universities and non-essential work places to limit people gathering in clusters must be done to break the chain of transmission. Some of the preventive measures include:

\*Wash hands thoroughly with soap and water or an alcohol based hand rub. This will kill the virus on your hands.

\*Maintain social distancing of at least 3 to 6 feet between yourself and anyone who is coughing or sneezing. This will prevent breathing of droplets from a sick person.

\*Avoid handshakes or kisses.

\*Avoid touching eyes, nose and mouth, because the hand touches many surfaces and can pick up viruses. Hands can transfer the virus to your eyes, nose or mouth facilitating its entry into the body.

\*Practice respiratory hygiene: This means covering your mouth and nose with your bent elbow, use tissue paper when you cough and sneeze, and then dispose the used tissue

immediately. By doing so, you can protect the people around you from virus transmission.

\*Early medical care in case of fever, cough or breathlessness.

Protection measures for person who are in or have recently visited (past 14 days) areas where Covid-19 is spreading:

\*Follow the guidelines outlined above

\*Stay at home if you begin to feel unwell even with mild symptoms such as headache and running nose, until you recover.

\*If you develop fever, cough or difficulty breathing, seek medical advice promptly.

### **Role of prophylaxis in Covid-19**

In vitro studies have shown that chloroquine and HCQ can inhibit the replication of SARS-CoV2. A multi-centric study in China concluded that chloroquine decreased the lung pathology and shortened the disease course without any serious adverse reactions [32]. In another Chinese study, HCQ was found to reduce the time to clinical recovery [33]. French studies have suggested that HCQ, especially in combination with azithromycin, can reduce the viral load in Covid-19 patients [34, 35]. These studies should have guided the Indian Council of Medical Research (ICMR) to recommend HCQ for chemoprophylaxis of Covid-19 in asymptomatic health workers and asymptomatic household contacts of confirmed patients. The recommended dose is 400 mg twice on day 1, followed by 400 mg once every week for 3 weeks and 7 weeks in case of asymptomatic household contacts and asymptomatic health workers respectively.

However, the RECOVERY trial and randomized control trial of HCQ as a part of prophylaxis for Covid-19 did not find any clinical benefit on hospital stay, 28 day mortality or prevention of Covid-19 infection after high or moderate risk exposure to SARS-CoV2 [36].

### **Is there any Vaccine against SARS-COV2?**

As a variety of Covid-19 vaccines are being developed around the world since the first publication of genomic structure of the virus from China on January 9, 2020. According to WHO, there are 48 vaccines in clinical trials and 164 candidate vaccines in preclinical evaluations by November 12, 2020. All vaccines stimulate primary immune response so that the body can develop memory B and T cells against the SARS-CoV 2 virus. The development of immune memory by vaccines will be protecting the person against subsequent Covid-19 infections. Monoclonal antibodies (Bamlanivimab), polyclonal antibodies (Regenerom), convalescent plasma and mRNA Induced antibody (M.I.T ) only produce passive immunity.

The types of vaccines being developed are:

\*Inactivated vaccines

\*Protein-based vaccines, which use harmless fragments of proteins or protein shells that mimic the Covid-19 virus and thereby generate an immune response.

\*Viral vector vaccines, which use a virus that has been genetically engineered so that it can't cause disease, but produces coronavirus proteins which can safely generate an immune response.

\*RNA and DNA vaccines that uses genetically engineered RNA or DNA to generate a protein that itself can prompt an immune response.

Scientists are also studying whether the Bacille Calmette-Guerin (BCG) vaccine, which is used to prevent tuberculosis, is effective against Covid-19.

Various types of vaccine are given in the chart below [37]:

(The name of the company is given in brackets)

VIRAL VACCINE	NUCLEIC ACID VACCINE	PROTEIN VACCINE
<b>1. Live attenuated vaccine</b> (Codagenix Vaccine by US BioTech Firm and Serum Institute of India)	<b>1. mRNA Vaccine</b> (Moderna Co, Pfizer of USA)	<b>1. Viral subunit Vaccines</b> (NovoVax, Adapt Vac, Clover Biopharma)
<b>2. Inactivated virus vaccine</b> (SinoVac & Bharath BioTech)	<b>2. Viral vector Vaccine</b> (Oxford/Astrazenica, Janssen, Gamaleya/Sputnik)	<b>2. Virus Like Particle Vaccine (VPL )</b>
	<b>3. DNA Vaccine (INOVIO)</b>	<b>3. Split Virus Vaccine</b>
		<b>4. RNP Vaccine (RibonucleoProtein)</b>

Each Covid-19 vaccine has distinct advantages and disadvantages , but development of different Covid-19 vaccines provides some overlaps. All vaccines have to undergo preclinical studies in cultured cells and animals to ensure effective immune response without being toxic. This is followed by Phase 1, Phase 2, Phase 3 clinical trials. Once available, the vaccine distribution follows the guidelines recommended by CDC (Centers for Disease Control and Prevention) and developed by the Advisory Committee on Immunization Practice (ACIP). CDC recommends vaccinating the highest risk populations first. A priority list is then placed out in each country. At present, mRNA vaccine by Pfizer and Moderna companies of USA have been sanctioned for vaccinating the people in the USA, UK and some other countries. Most of the vaccines produce 70-90% efficacy with some minor side effects. Pfizer company issued a warning against anaphylactoid reactions in some patients where vaccination may not be given [38]. We have to closely monitor the Phase 4 clinical

trials for assessing the total duration of the immunity after two doses of vaccine at 21 days interval. The world population can start to recover from the pandemic if herd immunity is obtained by vaccinating 60 % of the total population. We have to continue the standard precautions against Covid-19 to limit the spread of infection. At present virus has mutated several times and some variant strains like D614G and B.1.1.7 are making the virus capable of infecting more people without increasing the mortality.

## Conclusion

The SARS-CoV2 outbreak started in the last week of 2019 in Wuhan city of China. So far it has been reported in every continent except Antarctica. As on 20th September 2020, about 30.1 million are affected worldwide with 9,59,000 deaths. Looking back there was an outbreak of an unusual acute respiratory infection which originated from Guangdong province of South China (Severe Acute Respiratory Syndrome) by a similar virus in November 2002 which spread to almost 30 countries resulting in 800 deaths.

### *What lessons to be learned by the people and the Governments?*

South China and South East Asia are continuing to be hot spots emerging and re-emerging new infectious diseases. Urbanization and globalization must aim at sustainable development. Destruction of natural ecosystems and poaching of animals must be avoided. Climatic change especially global warming and deforestation might lead to emergence of new viruses and diseases. A change in the cultural habits of people is also required. One health policy i.e. animal husbandry, environment and human health must be under one department at the state, national and international level for early detection and containment of emerging zoonosis.

Even today we don't know exactly how long this Covid-19 pandemic is going to last. Will it disappear like SARS of 2003 or relapse periodically like influenza virus are questions yet to be answered?

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