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Coronavirus: An invisible lethal terror

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Abstract: There is a new public health crises threatening the world with the emergence and spread of 2019 novel coronavirus (2019-nCoV) or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus originated in bats and was transmitted to humans through yet unknown intermediary animals in Wuhan, capital city of Hubei province and a major transportation hub of China in December 2019. There have been around 22, 92, 93,200 reported cases of coronavirus disease 2019 (COVID-2019) and 47, 05,498 reported deaths to date (20/09/2021). The disease is transmitted by inhalation or contact with infected droplets and the incubation period ranges from 2 to 14 days. The symptoms are usually fever, cough, sore throat, breathlessness, fatigue, malaise among others. The disease is mild in most people; in some (usually the elderly and those with comorbidities), it may progress to pneumonia, acute respiratory distress syndrome (ARDS) and multi organ dysfunction. Many people are asymptomatic. Fortunately so far, children have been infrequently affected with no deaths. But the future course of this virus is unknown. Diagnosis is by demonstration of the virus in respiratory secretions by special molecular tests. Treatment is essentially supportive; role of antiviral agents is yet to be established. Prevention entails home isolation of suspected cases and those with mild illnesses and the treatment of patients with severe infection and symptoms is specially done at hospital that includes the treatment in ICU with strict control measures as per protocol guided by WHO. Few safe and effective vaccines discovered recently will prevent the illness after vaccination and save millions of lives. Beside this, wearing a mask, repeatedly washing hands and maintenance of social distance are the most important precautionary measures against COVID-19. The global impact of this new epidemic is yet uncertain.

Keywords: Coronavirus, 2019-nCoV, COVID-19

1. Introduction and Etymology

Coronaviruses are a group of retro- or RNA viruses that cause diseases in mammals. In humans, they cause respiratory tract infection that can range from mild to lethal. Mild illnesses in humans include some cases of the common cold (which is also caused by other viruses, predominantly rhinoviruses), while more lethal varieties can cause SARS (Sever Acute Respiratory Syndrome), MERS (Middle-East Respiratory Syndrome) and COVID-19 Corona Virus Disease -2019).

Viruses are actually ultramicroscopic, acellular, obligate parasite; they exhibit two distinct phases in their activity, such as extracellular phase and intracellular phase – in former phase viruses behave like non-living i.e. inanimate objects while in latter phase they behave like living organisms within the host-cells. Viruses contain single or double stranded either DNA or RNA, (as genetic material) but never both.

In December 2019, adults in Wuhan, capital city of Hubei province and a major transportation hub of China started to suffer from severe pneumonia of unknown cause and admitted to local hospitals. Many of the initial cases had a common exposure to the Huanan wholesale seafood market that also traded live animals.

The respiratory samples of patients were sent to reference laboratory for etiologic investigations. On December 31st 2019, China notified the outbreak to the World Health Organization and on 1st January the Huanan sea food market was closed. On 7 January the virus was identified as a novel coronavirus (2019-nCoV) that had >95% homology with the bat coronavirus and > 70% similarity with the SARS-CoV signifying that the virus originated from there [1]. This virus spreads faster than

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its two ancestors the SARS and MERS. The number of cases of coronavirus disease started increasing exponentially due to the fact of human-to-human transmission. The first fatal case was reported on 11th January 2020. The massive migration of Chinese during the Chinese New Year fuelled the epidemic. Cases in other provinces of China, other countries (Thailand, Japan and South Korea in quick succession) were reported in people who were returning from Wuhan. Transmission to healthcare workers caring for patients was described on 20th January, 2020. Cases of COVID-19 in countries outside China were reported in those with no history of travel to China suggesting that local human-to-human transmission was occurring in these countries [2]. Airports in different countries including India put in screening mechanisms to detect symptomatic people returning from China and placed them in isolation and testing them for COVID-19. Soon it was apparent that the infection could be transmitted from asymptomatic people and also before onset of symptoms. Therefore, countries including India who evacuated their citizens from Wuhan through special flights or had travellers returning from China placed all people symptomatic or otherwise in isolation for 14 days and tested them for the virus.

By 5th March, 2020, 29 cases had been reported; mostly in Delhi, Jaipur and Agra in Italian tourists and their contacts. One case was reported in an Indian who travelled back from Vienna and exposed a large number of school children in a birthday party at a city hotel. Many of the contacts of these cases have been quarantined.

These numbers are possibly an underestimate of the infected and dead due to limitations of surveillance and testing. Though the SARS-CoV-2 originated from bats, the intermediary animal through which it crossed over to humans is still unknown.

The name "coronavirus" is derived from Latin *corona*, meaning "crown" or "wreath" (Fig. 1). The name was coined by June Almeide and David Tyrrel who first observed and studied human coronaviruses [3]. The name refers to the characteristic appearance of virion (single infective form or particle of the virus) by electron microscopy, which has a fringe of large, bulbous surface projections creating an image of the *solar corona* or *halo* [1, 3]. This morphology is created by the viral protein spike.

This article gives a bird's eye view about this new virus. Since knowledge about this virus is rapidly evolving, readers are urged to update themselves regularly.

A B C

Fig. 1: *(A) Coronavirus, (B) Crown with spike and (C) Solar corona/halo during eclipse*

2. Origin of Human Coronavirus

Many human coronaviruses have their origin in bats (Fig. 2) [4]. The human coronavirus shared a common ancestor with a bat coronavirus [5]. MERS-CoV emerged in humans from bats through the intermediate host of camels [6]. MERS-CoV, although related to several bat coronavirus species, appears to have diverged from these several centuries ago [7] The ancestors of SARS-CoV first infected leaf-nose bats; subsequently, they spread to horseshoe bats, then to Asian palm civets, and finally to humans [8, 9]. The intermediary animal through which it crossed over to humans from bats is uncertain. Pangolins and snakes are the current suspects.

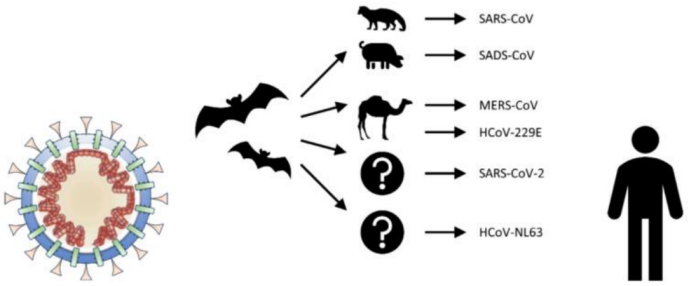

Fig. 2: *Origins of human coronaviruses with possible intermediate hosts*

3. Ultrastructure of Coronavirus

Coronaviruses are large, roughly spherical particles with unique spike-like surface projections [10]. Their size is highly variable with average diameters of 80 to 120nm. Extreme sizes are known from 50 to 200 nm in diameter [11]. The total molecular mass is on average 40,000kDa.

They are enclosed in an envelope embedded with a number of protein molecules [12]. The lipid bilayer envelope, membrane proteins, and nucleocapsid protect the virus when it is outside the host cell [13]. The viral envelope is made up of a lipid bilayer in which the membrane (M), envelope (E) and spike (S) structural proteins are anchored [14]. The molar ratio of E: S: M in the lipid bilayer is approximately 1:20:300 [15]. The E and M protein are the structural proteins that combined with the lipid bilayer to shape the viral envelope and maintain its size [16]. S proteins are needed for interaction with the host cells. The diameter of the envelope is 85 nm. The envelope of the virus in electron micrographs (Fig. 3) appears as a distinct pair of electron-dense shells (shells that are relatively opaque to the electron beam used to scan the virus particle) [17, 16].

The M protein is the main structural protein of the envelope that provides the overall shape and is a type III membrane protein. It consists of 218 to 263 amino acid residues and forms a layer 7.8 nm thick [11]. It has three domains, a short N-terminal ectodomain, a triple-spanning transmembrane domain, and a C-terminal endodomain. The C-terminal domain forms a matrix-like lattice that adds to the extra-thickness of the envelope. The M protein is crucial during the assembly, budding, envelope formation, and pathogenesis stages of the virus lifecycle [18].

The E proteins are minor structural proteins and highly variable in different species [10]. There are only about 20 copies of the E protein molecule in a coronavirus particle [14]. They are 8.4 to 12 kDa in size and are composed of 76 to 109 amino acids [10]. They are integral proteins (i.e. embedded in the lipid layer) and have two domains namely a transmembrane domain and an extramembrane C-terminal domain. They are almost fully α-helical, with a single α-helical transmembrane domain, and form pentameric (five-molecular) ion channels in the lipid bilayer (Fig. 4). They are responsible for virion assembly, intracellular trafficking and morphogenesis (budding) [11].

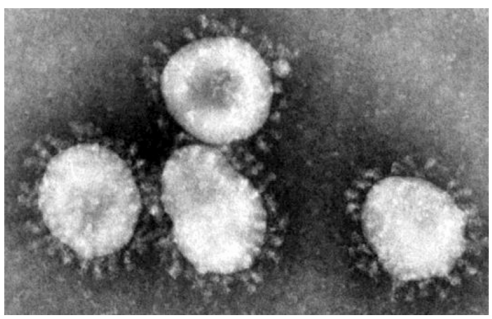

Fig. 3: *Transmission electron micrograph of coronaviruses*

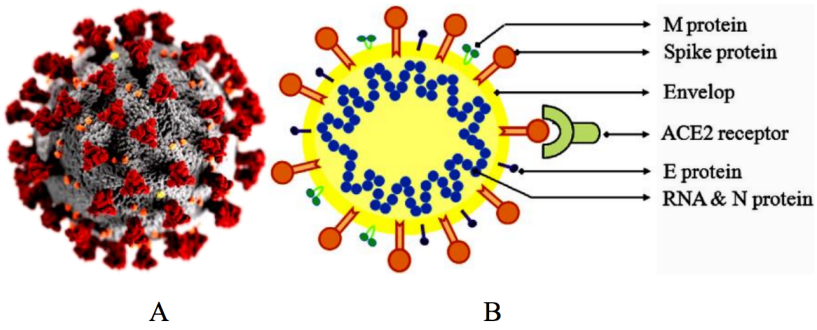

Fig. 4: *(A) Illustration of a coronavirus, (B) Diagrammatic view of the structure of coronavirus*

The spikes are the most distinguishing feature of coronaviruses and are responsible for the corona- or halo-like surface. On average a coronavirus particle has 74 surface spikes [19]. Each spike is about 20 nm long and is composed of a trimer of the S protein. The S protein is in turn composed of an S_1 and S_2 subunit. The homotrimeric S protein is a class I fusion protein which mediates the receptor binding and membrane fusion between the virus and host cell (Fig. 5). The S_1 subunit forms the head of the spike and has the receptor-binding domain (RBD). The S_2 subunit forms the stem which anchors the spike in the viral envelope and on protease activation enables fusion. The two subunits remain noncovalently linked as they are exposed on the viral surface until they attach to the host cell membrane [11]. In a functionally active state, three S_1 are attached to two S_2 subunits. The subunit complex is split into individual subunits when the virus binds and fuses with the host cell under the action of proteases such as cathepsin family and transmembrane protease serine 2 (TMPRSS2) of the host cell [20].

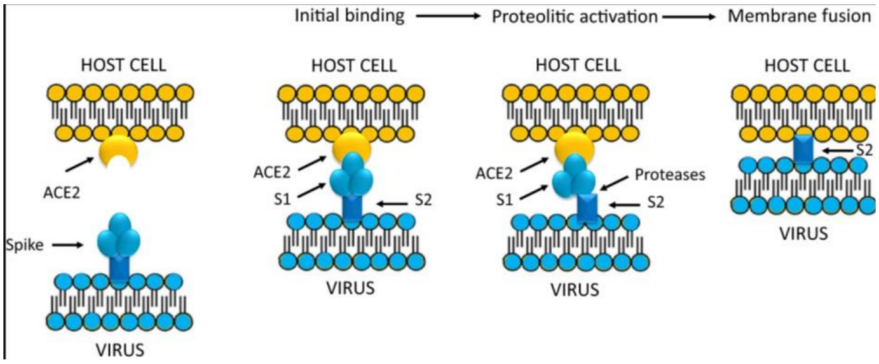

Fig.5 *After binding of the ACE2 receptor, coronavirus spike is activated and cleaved at the S1/S2 level*

S1 proteins are the most critical components in terms of infection. They are also the most variable components as they are responsible for host cell specificity. They possess two major domains named N-terminal domain (S1-NTD) and C-terminal domain (S1-CTD), both of which serve as the receptor-binding domains. The NTDs recognize and bind sugars on the surface of the host cell. S1-CTDs are responsible for recognizing different protein receptors such as angiotensin-converting enzyme 2 (ACE2), aminopeptidase N (APN), and dipeptidyl peptidase 4 (DPP4) [11].

Inside the envelope, there is the nucleocapsid, which is formed from multiple copies of the nucleocapsid (N) protein, which are bound to the positive-sense single-stranded RNA genome in a continuous beads-on-a-string type conformation (Fig. 6) [16, 21]. N protein is a phosphoprotein of 43 to 50 kDa in size, and is divided into three conserved domains. The majority of the protein is made up of domains 1 and 2, which are typically rich in arginines and lysines. Domain 3 has a short carboxy terminal end and has a net negative charge due to excess of acidic over basic amino acid residues [10].

Coronavirus contains a positive-sense, single-stranded RNA genome. Positive-strand RNA viruses (+ssRNA viruses) are a group of related viruses that have positive-sense, single-stranded genomes made of ribonucleic acid. The positive-sense genome can act as messenger RNA (mRNA) and can be directly translated into viral proteins by the host cell's ribosomes. Positive-strand RNA viruses encode an RNA-dependent RNA polymerase (RdRp) which is used during replication of the genome to synthesize a negative-sense anti-genome that is then used as a template to create a new positive-sense viral genome.

The genome size for coronaviruse is 30 kilobases [22]. The genome has a 5′ methylated cap and a 3′ polyadenylated tail [16].

The genome organization for a coronavirus is 5′-leader-UTR-replicase (ORF1ab)-spike (S)-envelope (E)-membrane (M)-nucleocapsid (N)-3′UTR-poly (A) tail. The open reading frames 1a and 1b, which occupy the first two-thirds of the genome, encode the replicase polyprotein (pp1ab). The replicase polyprotein self cleaves to form 16 non-structural proteins (nsp1–nsp16) [16].
The later reading frames encode the four major structural proteins: spike, envelope, membrane, and nucleocapsid [23]. Interspersed between these reading frames are the reading frames for the accessory proteins. The number of accessory proteins and their function is unique depending on the specific coronavirus [16].

4. Entry of Coronavirus causing infection in Human body

All ages are susceptible. Infection is transmitted through watery droplets (diameter = 0.5-12μ) generated during coughing and sneezing (contains 40,000 droplets per sneezing) by symptomatic patients but also occurs from asymptomatic people and before onset of symptoms [24]. Studies have shown higher viral loads in the nasal cavity as compared to the throat with no difference in viral burden between symptomatic and asymptomatic people [25]. Patients can be infectious for as long as the symptoms last and even on clinical recovery. The virus can remain viable on surfaces for days in favourable atmospheric conditions but are destroyed in less than a minute by common disinfectants like sodium hypochlorite, hydrogen peroxide etc. [26]. Infection is acquired either by inhalation of these droplets through nose or touching surfaces contaminated by them or then touching the nose, mouth and eyes. The virus is also present in the stool and contamination of the water supply and subsequent transmission via aerosolization/feco oral route is also hypothesized [27]. As per current information, transplacental transmission from pregnant women to their fetus has not been described [28]. However, neonatal disease due to post natal transmission is described [28]. The incubation period varies from 2 to 14 days.

Human coronaviruses mainly infect the epithelial cells of the respiratory tract and also a wide range of cells and systems of the body, while animal coronaviruses generally infect the epithelial cells of the digestive tract [29].

Coronavirus infects the human epithelial cells of the lungs via an aerosol route [30]. Studies have identified angiotensin receptor 2 (ACE_2) as the receptor through which the virus enters the respiratory mucosa [31]. Coronavirus is most known for affecting the upper respiratory tract (sinuses, nose, and throat) and the lower respiratory tract (windpipe and lungs) [32]. The lungs are the organs most affected by coronavirus because the virus accesses host cells via the receptor for the enzyme angiotensin-converting enzyme 2 (ACE2), which is most abundant on the surface of type II alveolar cells of the lungs [33]. Infection begins when the viral spike glycoprotein attaches to its complementary host cell receptor. After attachment, a protease of the host cell cleaves and activates the receptor-attached spike protein and allows the virus to enter the host cell by endocytosis or direct fusion of the viral envelope with the host membrane [34].

On entry into the host cell, the virus particle is uncoated, and its genome enters the cell cytoplasm. Finally it hijacks the entire cellular machinery of the host cell. The coronavirus RNA genome has a 5′ methylated cap and a 3′ polyadenylated tail, which allows it to act like a messenger RNA and be directly translated by the host cell's ribosome. The host ribosomes translate the initial overlapping open reading frames ORF1a and ORF1b of the virus genome into two large overlapping polyproteins, pp1a and pp1ab [35].

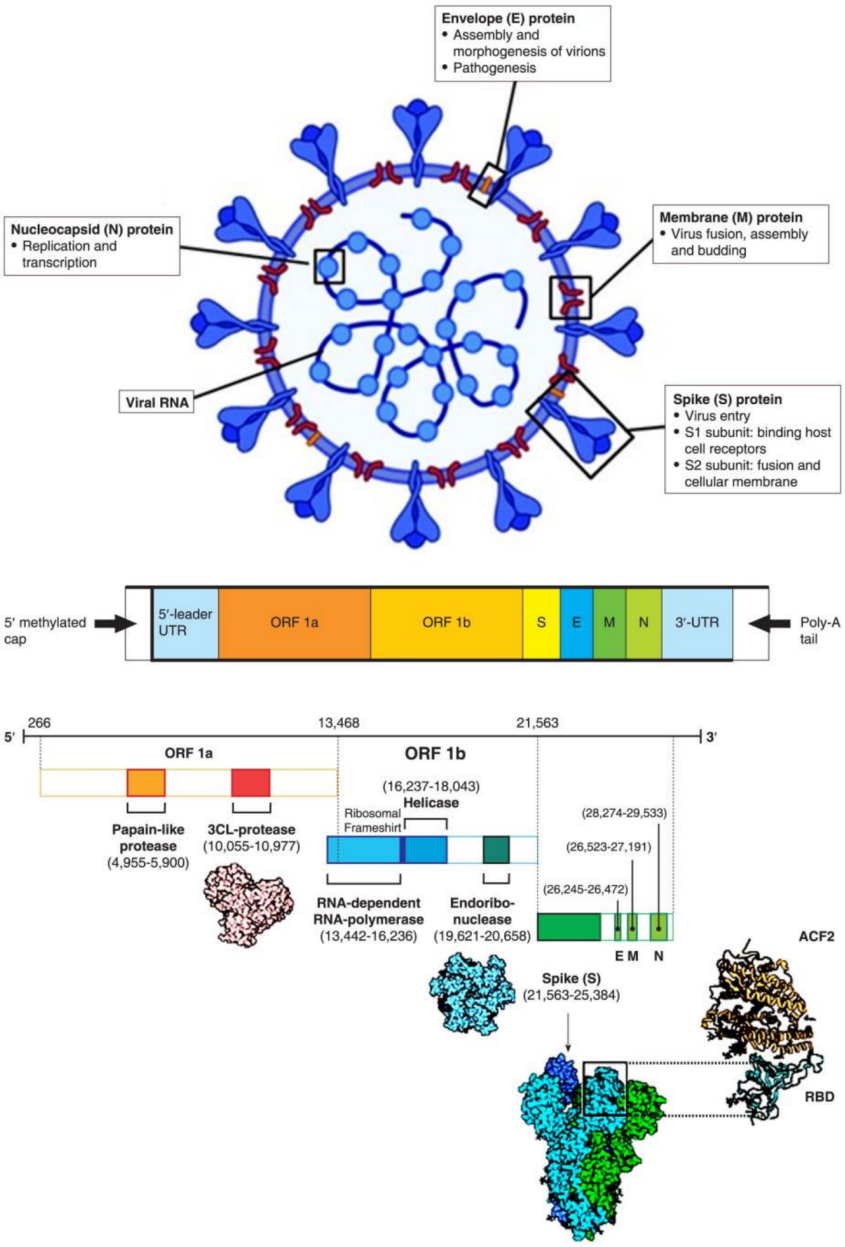

Fig. 6: *Diagrammatic view of the structure of coronavirus and its genome structure in details*

The larger polyprotein pp1-ab is a result of a -1 ribosomal frameshift caused by a slippery sequence (UUUAAAC) and a downstream RNA pseudo-knot at the end of open reading frame ORF1a [36]. The ribosomal frameshift allows for the continuous translation of ORF1a followed by ORF1b [35].

The polyproteins have their own proteases, PLpro(nsp3) and 3CLpro (nsp5), which cleave the polyproteins at different specific sites. The cleavage of polyprotein pp1ab yields 16 nonstructural proteins (nsp1 to nsp16). Product proteins include various replication proteins such as RNA-dependent RNA polymerase (nsp12),helicase (nsp13), and exoribonuclease (nsp14) [35].

A number of the nonstructural proteins coalesce to form a multi-protein replicase-transcriptase complex. The main replicase-transcriptase protein is the RNA-dependent RNA polymerase (RdRp). It is directly involved in the replication and transcription of RNA from an RNA

strand. The other nonstructural proteins in the complex assist in the replication and transcription process.

One of the main functions of the complex is to replicate the viral genome. RdRp directly mediates the synthesis of negative-sense genomic RNA from the positive-sense genomic RNA. This is followed by the replication of positive-sense genomic RNA from the negative-sense genomic RNA [35].

The replicated positive-sense genomic RNA becomes the genome of the progeny viruses. The mRNAs are gene transcripts of the last third of the virus genome after the initial overlapping reading frame. These mRNAs are translated by the host's ribosomes into the structural proteins and many accessory proteins [35]. RNA translation occurs inside the endoplasmic reticulum. The viral structural proteins S, E, and M move along the secretory pathway into the Golgi intermediate compartment. There, the M proteins direct most protein-protein interactions required for the assembly of viruses following its binding to the nucleocapsid. Progeny viruses are then released from the host cell by exocytosis through secretory vesicles. Once released, the viruses can infect other healthy host cells [37]. The virus may also enter the bloodstream from the lungs and is able to spread and invade to also a wide range of cells and systems of the body through blood. In severe COVID-19 cases, lung cells are damaged and the lung shows the patches of lesions (Fig. 7) in the lung.

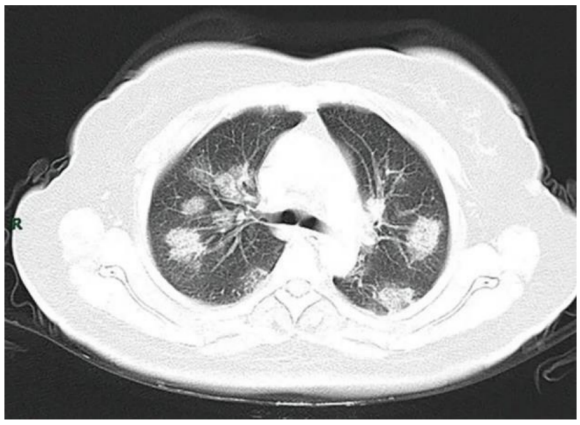

Fig. 7: *A CT scan of a patient with COVID-19 shows lesions (bright regions) in the lungs*

Most people who get COVID-19 have mild or moderate symptoms like coughing, a fever, and shortness of breath. But some who catch the new coronavirus get severe pneumonia (Fig. 8) in both lungs. COVID-19 pneumonia is a serious illness that can be deadly. Pneumonia is a lung infection that causes inflammation in the tiny air sacs inside your lungs. They may fill up with so much fluid and pus that it’s hard to breathe and the patient may have severe shortness of breath, a cough, a fever, chest pain, chills, or fatigue.

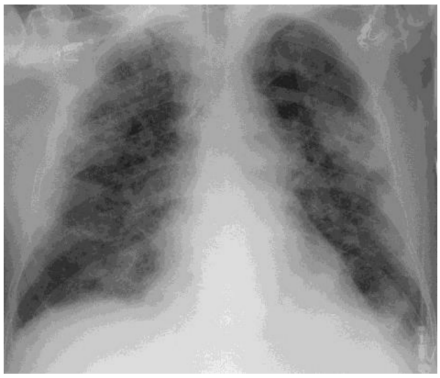

Fig. 8: *Chest X-ray showing COVID-19 pneumonia*

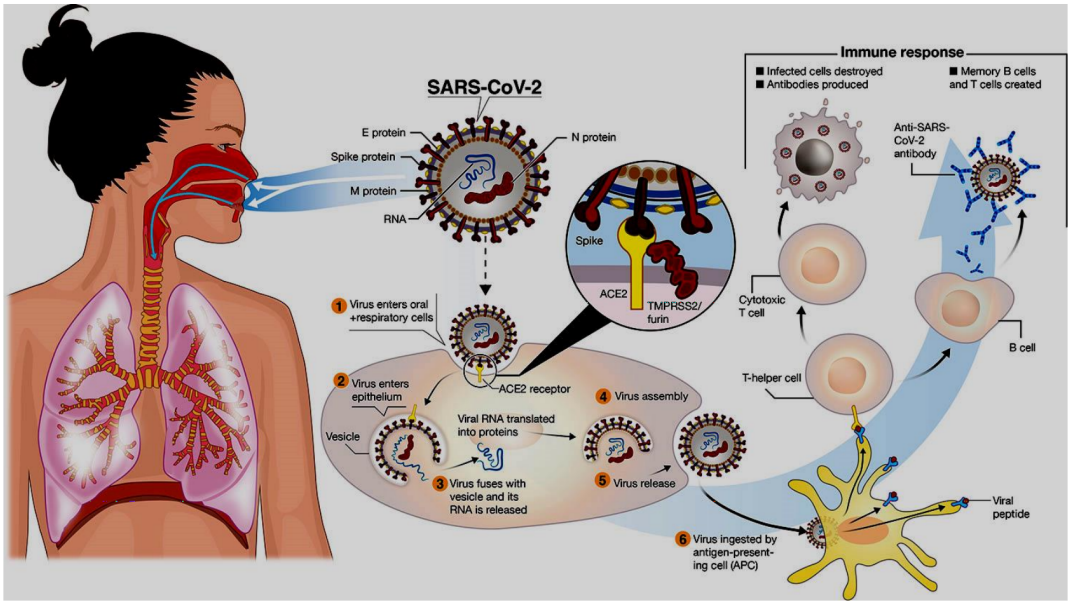

Fig. 9: *Transmission and life-cycle of coronavirus causing COVID-19*

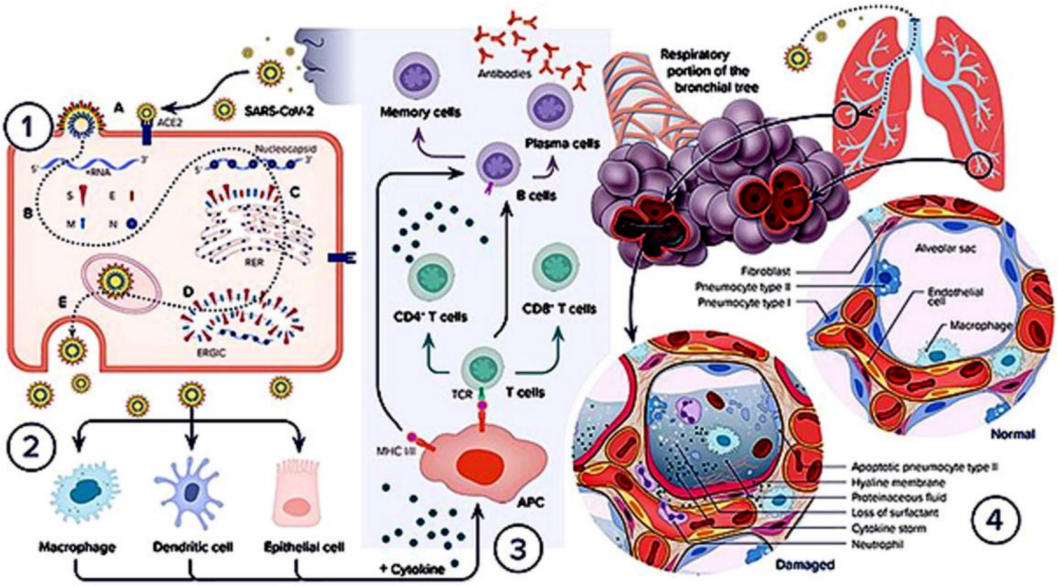

Fig. 10: *Pathogenesis of coronavirus: (1) coronavirus enters the epithelial cell and gets released after completing their life cycle; (2) infection induces inflammatory factors; (3) Antigen presentation of coronavirus and (4) in severe COVID-19 cases, the virus reaches the lower respiratory tract*

Coronavirus infection induces inflammatory factors that lead to activation of macrophages and dendritic cells (Fig. 9). Antigen presentation of coronavirus via major histocompatibility complexes I and II (MHC I and II) stimulates humoral and cellular immunity resulting in cytokine and antibody production. . In severe COVID-19 cases, the virus reaches the lower respiratory tract and infects type II pneumocytes leading to apoptosis and loss of surfactant. The influx of macrophages and neutrophils induces a cytokine storm. A cytokine storm can be a complication in the later stages of severe COVID-19. A cytokine storm is a potentially deadly immune reaction where a large amount of pro-inflammatory cytokines and chemokines are released too quickly; a cytokine storm can lead to ARDS and multiple organ failure [38]. China indicates that patients who had more severe responses to

COVID-19 had greater amounts of pro-inflammatory cytokines and chemokines in their system than patients who had milder responses; these high levels of pro-inflammatory cytokines and chemokines indicate presence of a cytokine storm [39]. Leaky capillaries lead to alveolar edema. Hyaline membrane is formed. All of these pathological changes result in alveolar damage and collapse, impairing gas exchange.

The immune response (Fig. 10) by humans to coronavirus occurs as a combination of the cell-mediated immunity and antibody production [40], just as with most other infections [41]. B cells interact with T cells and begin dividing before selection into the plasma cell, partly on the basis of their affinity for antigen [42]. The presence of neutralizing antibodies in blood strongly correlates with protection from infection, but the level of neutralizing antibody declines with time. Those with asymptomatic or mild disease had undetectable levels of neutralizing antibody two months after infection. In another study, the level of neutralizing antibodies fell four-fold one to four months after the onset of symptoms. However, the lack of antibodies in the blood does not mean antibodies will not be rapidly produced upon re-exposure to coronavirus. Memory B cells specific for the spike and nucleocapsid proteins of corona last for at least six months after the appearance of symptoms [43].

Whether coronavirus is able to invade the nervous system remains unknown. However, it is clear that many people with COVID-19 exhibit neurological or mental health issues. The virus is not detected in the CNS (Central Nervous System) of the majority of COVID-19 people with neurological issues. However, coronavirus has been detected at low levels in the brains of those who have died from COVID-19, but these results need to be confirmed [44]. Loss of smell results from infection of the support cells of the olfactory epithelium, with subsequent damage to the olfactory neurons [45]. coronavirus could cause respiratory failure through affecting the brain stem as other coronaviruses have been found to invade the CNS. While virus has been detected in cerebrospinal fluid of autopsies, the exact mechanism by which it invades the CNS remains unclear and may first involve invasion of peripheral nerves given the low levels of ACE2 in the brain [46, 47, 48]. The virus may also enter the bloodstream from the lungs and cross the blood-brain barrier to gain access to the CNS, possibly within an infected white blood cell [44].

The coronavirus also affects gastrointestinal organs as ACE2 is abundantly expressed in the glandular cells of gastric, duodenal and rectal epithelium [49]as well as endothelial cells and enterocytes of the small intestine [50].

The coronavirus can cause acute myocardial injury and chronic damage to the cardiovascular system [51]. Rates of cardiovascular symptoms are high, owing to the systemic inflammatory response and immune system disorders during disease progression, but acute myocardial injuries may also be related to ACE2 receptors in the heart.[51] ACE2 receptors are highly expressed in the heart and are involved in heart function[51,52] A high incidence of thrombosis and venous thromboembolism have been found in people transferred to Intensive care units (ICU) with COVID-19 infections. Blood vessel dysfunction and clot formation are thought to play a significant role in mortality, incidences of clots leading to pulmonary embolisms, and ischemic events within the brain have been noted as complications leading to death in people infected with SARS-CoV-2. Infection appears to set off a chain of vasoconstrictive responses within the body, constriction of blood vessels within the pulmonary circulation has also been posited as a mechanism in which oxygenation decreases alongside the presentation of viral pneumonia [53]. Furthermore, micro vascular (arterioles and capillaries) blood vessel damage has been reported in a small number of tissue samples of the brains – without detected SARS-CoV-2 – and the olfactory bulbs from those who have died from COVID-19 [54,55,56]. COVID-19 was also found to cause substantial – including morphological and mechanical – changes to blood cells – such as increased sizes – sometimes persisting for months after hospital discharge [57, 58].

Another common cause of death is complications related to the kidneys [59]. Early reports show that up to 30% of hospitalized patients both in China and in New York have experienced some injury to their kidneys, including some persons with no previous kidney problems [60].

Biological factors (immune response) and the general behaviour (habits) can strongly determine the consequences of COVID-19 [61]. Most of those who die of COVID-19, have pre-existing (underlying) conditions, including hypertension, diabetes mellitus, and cardiovascular disease [62]. The most common comorbidities are hypertension (66% of deaths), type 2 diabetes (29.8% of

deaths), Ischemic Heart Disease (27.6% of deaths), atrial fibrillation (23.1% of deaths) and chronic renal failure (20.2% of deaths).

Most critical respiratory comorbidities are: moderate or severe asthma, pre-existing COPD (Chronic Obstructive Pulmonary Disease), pulmonary fibrosis, cystic fibrosis [63]. Smoking can be associated with worse outcomes [64, 65].

5. Symptoms of COVID-19

COVID-19 affects different people in different ways. Most infected people will develop symptoms of COVID-19 which are variable, ranging from mild symptoms to severe illness.

(i) Most common symptoms:

Fever
Cough
Tiredness
Loss of taste or smell

(ii) Less common symptoms:

Sore throat
Headache
Aches and pains
Diarrhoea
A rash on skin, or discolouration of fingers or toes
Red or irritated eyes

(iii) Serious symptoms:

Difficulty breathing or shortness of breath
Loss of speech or mobility, or confusion
Chest pain
Acute respiratory distress syndrome (ARDS)

People with mild symptoms who are otherwise healthy should manage their symptoms at home.

On average it takes 5–6 days from when someone is infected with the virus for symptoms to show, however it can take up to 14 days. Of people who show symptoms, 81% develop only mild to moderate symptoms (up to mild pneumonia), while 14% develop severe symptoms (dyspnea, hypoxia, or more than 50% lung involvement on imaging) and 5% of patients suffer critical symptoms (respiratory failure, shock, or multiorgan dysfunction) [66]. At least a third of the people who are infected with the virus do not develop noticeable symptoms at any point in time [67, 68]. These asymptomatic carriers tend not to get tested and can spread the disease [68, 69, 70, 71]. Other infected people will develop symptoms later, called "pre-symptomatic", or have very mild symptoms and can also spread the virus [71].

Most of those who die of COVID-19 have pre-existing (underlying) conditions or the most common comorbidities like hypertension (66% of deaths), type 2 diabetes (29.8% of deaths), Ischemic Heart Disease (27.6% of deaths), atrial fibrillation (23.1% of deaths) and chronic renal failure (20.2% of deaths) moderate or severe asthma, pre-existing COPD ((Chronic Obstructive Pulmonary Disease), pulmonary fibrosis, cystic fibrosis. When someone with existing respiratory problems is infected with COVID-19, they might be at greater risk for severe symptoms [72]. Several research papers also suggest that smoking can be associated with worse outcomes [73, 74]. CDC (The Centers for Disease Control and Prevention) issued a caution that tuberculosis (TB) infections could increase the risk of severe illness or death with COVID-19. COVID-19 also poses a greater risk to

people who opioids and methamphetamines, insofar as their drug use may have caused lung damage [75].

Pregnant women who do get infected with coronavirus are more likely to have a severe illness than women who aren't pregnant. There's not enough research yet to know if coronavirus can spread to babies during pregnancy or birth. The virus has not been found in amniotic fluid or breast milk, but some babies born to mothers with coronavirus have tested positive for the virus. Newborns can catch the virus from an infected parent. The CDC says it's unlikely that the virus can pass from a mother with confirmed COVID-19 to her unborn baby (a process known as vertical transmission).Research on COVID-19 is still ongoing, but one small study published in December 2020 supports this: Researchers looked at women who tested positive for the coronavirus in their third trimester and found no signs of the virus in maternal or cord blood or in the placenta, and no evidence of viral transmission to the newborn. Some experts suggest that children might not be as severely affected by COVID-19 because there are other viruses that spread in the community and cause diseases such as the common cold. Since children often get colds, their immune systems might be primed to provide them with some protection against COVID-19. It's also possible that children's immune systems interact with the virus differently than do adults' immune systems.

Angiotensin converting enzyme 2 (ACE2) is the main receptor for the entry of SARS-CoV-2 into human cells. This receptor is present on many cells including epithelial cells of the nasopharynx, lungs, heart, kidney, intestine, liver, testis, placenta, central nervous system and blood vessels, as well as macrophages. Furthermore, it has also been postulated that children have ACE2 receptors with a lower affinity for SARS-CoV-2 and a different distribution across body sites, making the entry of SARS-CoV-2 into cells more difficult.

In addition to the ACE2 receptor, SARS-CoV-2 entry into cells involves transmembrane serine protease 2 (TMPRSS2), which cleaves the viral spike protein. TMPRSS2 is absent among children and has been reported to increase with age on nasal and lung epithelial cells. So, babies and children remain protected and react negatively to COVID-19.

There is a common question among layman why are some people infected with COVID-19 asymptomatic? Researchers worldwide have been surprised to see that individuals can be infected with the virus that produces COVID-19 - without showing symptoms. Since these individuals expose others to infection without knowing it, it is important to find an explanation.

On the inside of our lungs are specialized immune cells, called alveolar macrophages, which help maintain a healthy environment in the lungs. The lungs contain a large number of alveolar macrophages, so they are probably also the first cell type an invading virus encounters. When the body recognizes a viral infection, our immune system initiates the production of interferons. Interferons are a group of cytokines that help shape the immune response and are therefore essential in the fight against viral infection. Alveolar macrophages have previously been shown to produce large amounts of interferons upon infection with respiratory viruses. Coronavirus is a respiratory virus that typically infects the outermost cell layer of the lungs, the epithelial layer. New research has shown that interferon production in the infected epithelial cells can be inhibited by the SARS-CoV-2 virus. This result is the low interferon production and therefore also a limited activation of the immune system to fight against the virus. Although the epithelial layer is the target of the virus, it must be assumed that the first cell type the virus encounters is the alveolar macrophages, and therefore these cells are important for how quickly an immune response to a SARS-CoV-2 infection can be initiated. Those people, whose alveolar macrophages response is very fast, become asymptomatic.

6. COVID-19 testing

The WHO has published several testing protocols for COVID-19. Besides the suspected cases, the COVID-19 test should do on all people for screening the actual number of infected cases in a place o rcountry. There are several methods for detecting corona infected person. But the most reliable, effective and specific diagnosis is by specific molecular tests known as reverse transcription.

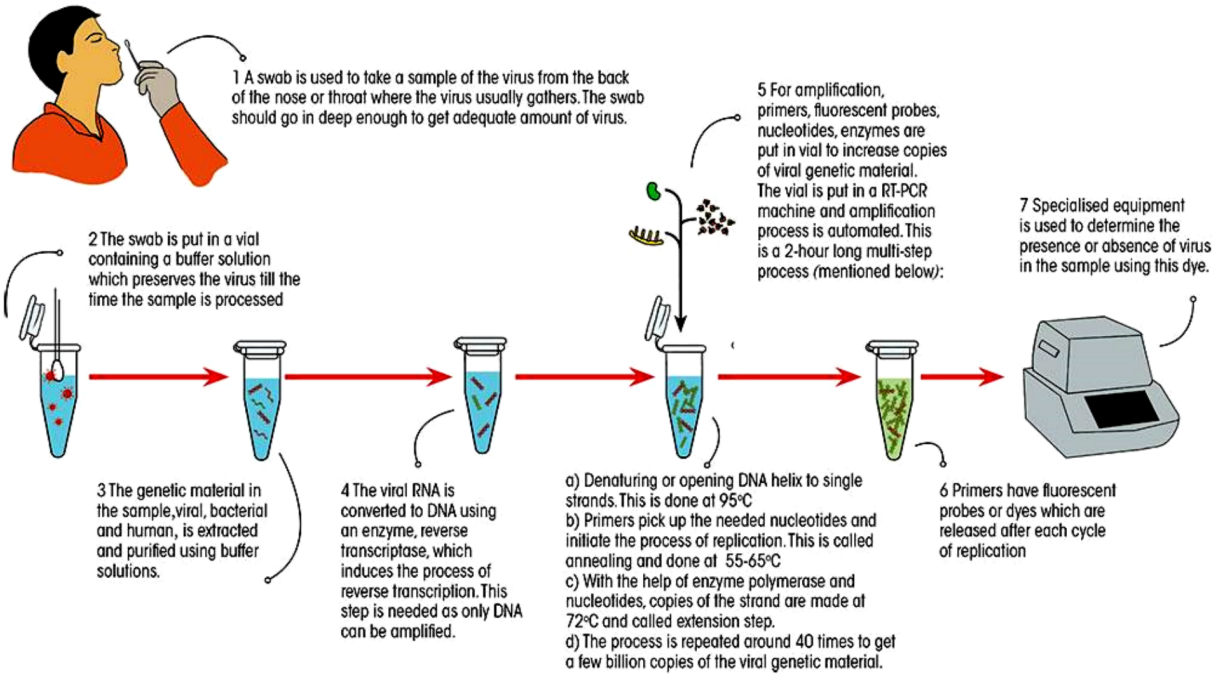

Fig.11: *Flow diagram of RT-PCR technique for diagnosis of COVID-19*

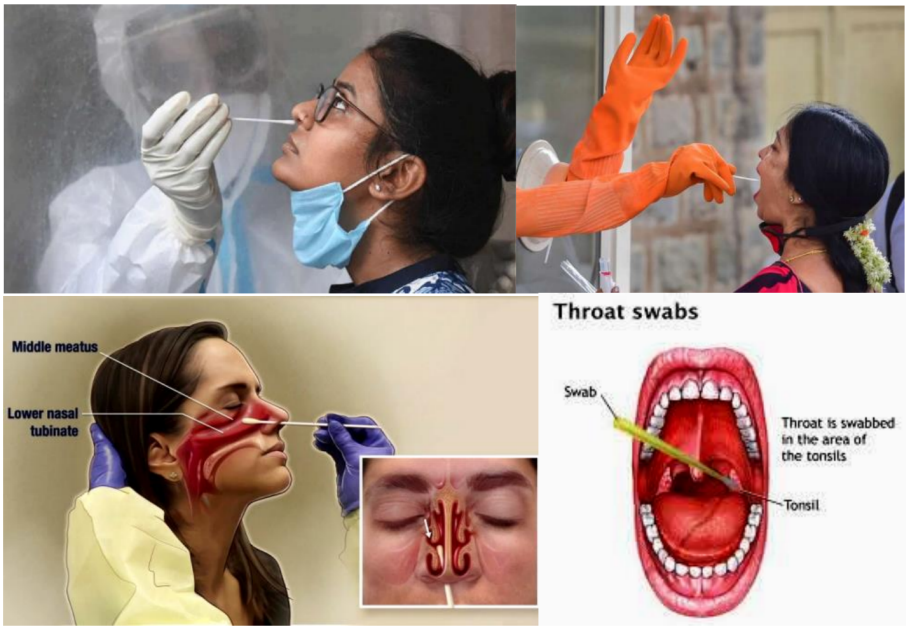

Fig.12: *Collection of swabs from nasopharyngeal or throat regions for diagnosis of COVID-19*

polymerase chain reaction (RT-PCR) (Fig. 11). This test is done from the respiratory samples obtained by a nasopharyngeal swab (Fig. 12). However, throat swab, sputum, endotracheal aspirates and bronchoalveolar lavage sample may also be used [76, 77]. Sensitivity of clinical samples by RT-PCR is 63% for nasal swab, 32% for pharyngeal swab, 48% for faeces, 72–75% for sputum, and 93–95% for bronchoalveolar lavage [78].

Reverse transcription or real time (the actual time during which a process takes place or an event occurs) polymerase chain reaction (RT-PCR) first uses reverse transcription to obtain DNA, followed by PCR to amplify that a small, well-defined segment of DNA many hundreds of thousands of times, creating enough of it for analysis. Test samples are treated with certain chemicals [79, 80] that allow DNA to be extracted. Reverse transcription converts RNA into DNA. The RT-PCR process generally requires a few hours [81]. These tests are also referred to as molecular or genetic assays [82].

This test detects the presence of viral RNA if present in the sample, but not infectious virus. The sample is treated with several chemical solutions that remove substances such as proteins and fats and that extract only the RNA present in the sample.

The viralRNA is reverse transcribed to viralDNA using a specific enzyme known as reverse transcriptase (RT). It is also known as RNA-dependent DNA polymerase that is a DNA polymerase enzyme that transcribes single-stranded viral RNA into viral DNA.

The viral DNA is then placed in an RT–PCR machine or thermocycler. The machine cycles through temperatures that heat and cools the viral DNA to trigger specific chemical reactions that create new, identical copies of the target sections of viral DNA. The cycle is repeated over and over to continue copying the viral DNA. Each cycle doubles the previous number: two copies become four; four copies become eight, and so on. A standard real time RT–PCR set-up usually goes through 40 cycles, which means that, by the end of the process, around a few billion new copies of the viral DNA are created from each strand of the virus present in the sample. For the amplification or doubling of copies of viral DNA, a specialized heat stable enzyme known as *taq* polymerase and a primer are essentially needed. As new copies of the viral DNA are built, the marker labels attach to the DNA strands and then release a fluorescent dye, which is measured by the machine's computer and presented in real time on the screen. The computer tracks the amount of fluorescence in the sample after each cycle. When a certain level of fluorescence is surpassed, this confirms that the virus is present. The suspected case is then diagnosed and confirmed as corona positive case.

7. Treatment

There is no specific, effective treatment or cure for coronavirus disease 2019 (COVID-19).Treatment is essentially supportive and symptomatic. The first step for a suspected corona patient is to ensure adequate isolation to prevent transmission to other healthy people and family members. Mild illness should be managed at home with thorough counselling about danger signs. The usual principles are maintaining hydration and nutrition and controlling fever and cough. Body's oxygen level of the patient is frequently checked by digital oxymeter. If the oxygen level goes beyond 92, the patient is immediately given oxygen support or the patient is immediately admitted to hospital for non-invasive ventilation. Paracetamol medicine is given to the patients to relieve symptoms like fever, body ache, cough etc. Antibiotics and antifungals medicines are also given to suppress the co-infections. Zinc tablets. Vitamin C tablets and multivitamins are also used as supportive medicines to improve the status of body's immunity. Among some hospitalised patients with COVID-19, a few corticosteroid drugs were applied for clinical trials in a wide range of conditions for its anti-inflammatory and immunosuppressant effects. Recovery was found to have benefits for critically ill patients. However, the role of corticosteroids is unproven; while current international consensus and WHO advocate against their use, Chinese guidelines do recommend short term therapy with low-to-moderate dose corticosteroids in COVID-19 ARDS [83, 84]. Some antiviral drugs such as ribavirin, lopinavir-ritonavir have been used based on the experience with SARS and MERS. Remdesivir, a broad spectrum anti RNA drug developed for Ebola in management of COVID-19 [85] was approved or authorized for emergency use to treat COVID-19 in around 50 countries. Remdesivir acts as a nucleoside analog and inhibits the RNA-dependent RNA polymerase (RdRp) of coronaviruses including SARS-CoV-2. Remdesivir is incorporated by the RdRp into the growing RNA product and allows for addition of three more nucleotides before RNA synthesis stalls. There is, as of now, no approved treatment for COVID-19.

A group of Chinese scientists report the isolation of two human monoclonal antibodies with the potential to treat and to prevent SARS-CoV-2 infections, the causative agent of COVID-19.

Monoclonal antibodies are identical copies of an antibody that targets one specific antigen. Scientists can make monoclonal antibodies experimentally by exposing white blood cells to a particular antigen. They can then select a single white blood cell or clone and use this as the basis to produce many identical cells, making many identical copies of the monoclonal antibody. The two monoclonal antibodies block binding of the spike protein of the virus to the host cell's receptor preventing entry. Such antibodies hold great promise for treatment as they are expected to prevent the virus spreading from cell to cell and have their strong ability to resist the virus. This drug is administered intravenously.

8. Prevention

The well known phrase is "prevention is better than cure". Since COVID-19 has no effective treatment and definite control measure to reduce the chances of infection, so it is better to take some important preventive measures so that we can keep ourselves safe and avoid the disease. Effective preventive measures against COVID-19 are as follows:

1. Staying at home during pandemic situation and lockdown period or containment areas declared by government.
2. Wearing a face mask, hand gloves and head cap in public.
3. Maintain 2 meters social or physical distance from others, avoid crowed places
4. Use hand sanitizer and wash hands frequently with hand wash or soap and water for at least twenty seconds.
5. Ventilate indoor space
6. Avoid touching the eyes, nose or mouth with unwashed hands.
7. Convalescent plasma therapy and COVID-19 vaccines.

In view of the rising number of Covid-19 cases, Lockdown (closing of market, shops, institution, office and transports) period is generally declared by the government of any country to block the transmission of the virus and by this orders it limits the movement of the entire population of a country for certain period as a preventive measure against the COVID-19 pandemic. According to the Union Ministry for Health and Family Welfare, containment zones are specific geographic areas where Covid-19 positive cases are found in large numbers. Such zones are identified by the government and local transmission is prevented.

The WHO and the US CDC recommend individuals wear non-medical face coverings in public settings where there is an increased risk of transmission and where social distancing measures are difficult to maintain [86,87]. This recommendation is meant to reduce the spread of the disease by asymptomatic and pre-symptomatic individuals and is complementary to established preventive measures such as social distancing [87, 88]. Face coverings limit the volume and travel distance of expiratory droplets dispersed when talking, breathing, and coughing [87,88]. A face covering will also filter out particles containing the virus from inhaled and exhaled air, reducing the chances of infection [89]. Many countries and local jurisdictions encourage or mandate the use of face masks or cloth face coverings by members of the public to limit the spread of the virus [90]. When in any room or vehicle with another person, cover coughs and sneezes with a tissue, regularly wash hands with soap and water and avoid sharing personal household items [91, 92]. , The CDC recommends the use of N95 type of mask. N stands for "Non-Oil" meaning that if no oil-based particulates are present, then you can use the mask in the work environment. Masks ending in a 95 have 95 percent efficiency.

During the COVID-19 pandemic, social distancing measures have been implemented nearly worldwide in order to slow the spread of the disease. Social distancing, or physical distancing,[93,94,95] is a set of non-pharmaceutical interventions or measures taken to prevent the spread of a contagious disease by maintaining a physical distance between people and reducing the number of times people come into close contact with each other[93,96]. It involves keeping a distance of six feet or two meters from others and avoiding gathering together in large groups [97, 98]. During the COVID-19 pandemic, social distancing and related measures were emphasised by several governments as alternatives to an enforced quarantine of heavily affected areas.

Our unwashed hands are a critical vector for transmitting microorganisms. So, hand washing with soap and water for at least 20 s or the use of alcohol-based (60%) hand sanitizers when soap and

water are not available is the first line of defence in stopping the spread of infection. Hand washing should be done before or after: touching eyes, nose or mouth, touching masks, entering and leaving a public place, touching an item or surface that may be frequently touched by other people such as door handles, tables, gas pumps, shopping carts, mobile or keyboard of computer etc.

Ventilation is the process of introducing fresh air into indoor spaces while removing stale air. Letting fresh air into indoor spaces can help remove air that contains virus particles and prevent the spread of coronavirus (COVID-19). Opening windows and doors (when the weather permits) increases the outdoor ventilation rate in a room. Ensuring proper ventilation with outside air can help reduce indoor airborne contaminants, including SARS-CoV-2, the virus that causes COVID-19, and other viruses. To help prevent infections, keep the hands away from eyes, nose, and mouth especially during the COVID-19 pandemic. Why? The mucous membranes of such organs are a portal of entry for germs that cause respiratory infections, including COVID-19.

It is estimated that people touch their face about 23 times per hour! Respiratory infections can be caused by many different bacteria and viruses, including the virus that causes COVID-19. When anybody touches face, the germs on hands can take up residence in the mucous membranes and cause infections, including COVID-19 infections.

Respiratory infections, like pneumonia, flu, or COVID-19, can spread through droplets in the air when a sick person coughs, sneezes, or talks near others. They can also spread by direct contact with bacteria, viruses, and other disease-causing germs. When we touch people who are sick, or touch dirty surfaces, we contaminate our hands with germs. We can then infect ourselves with those germs by touching our face.

Convalescent plasma therapy and COVID-19 vaccines are used as a preventive measure to protect the majority of people from hospitalisation and death from COVID-19. Before the discovery of COVID-19 vaccine, convalescent plasma therapy uses blood from people who've recovered from an illness to help others recover. Transferring purified and concentrated antibodies produced by the immune systems of those who have recovered from COVID-19 to people who need them is being investigated as a non-vaccine method of passive immunisation. Viral neutralization is the anticipated mechanism of action by which passive antibody therapy can mediate defence against SARS-CoV-2.

A COVID-19 vaccine is a vaccine intended to provide acquired immunity against coronavirus that causes coronavirus disease 2019 (COVID-19).The COVID-19 vaccines are widely credited for their role in reducing the spread, severity, and death caused by COVID-19. As of 13 October 2021, 6.56 billion doses of COVID-19 vaccines have been administered worldwide based on official reports from national public health agencies. At the initial stage of COVID-19, there was no vaccine existed for preventing a coronavirus infection in humans. Scientists throughout the world were trying to develop an effective and safe vaccine, but all were in trial. As with all medicines, every vaccine must go through extensive and rigorous testing to ensure it is safe before it can be introduced in a country's vaccine programme.

Each vaccine under development must first undergo screenings and evaluations to determine which antigen should be used to invoke an immune response. This preclinical phase is done without testing on humans. An experimental vaccine is first tested in animals to evaluate its safety and potential to prevent disease. If the vaccine triggers an immune response, it is then tested in human clinical trials in three phases. The entire process takes long time and after that it is sent to government for its approval for large scale production and marketing. A vaccine forces our immune system to make antibodies against a specific disease. Then, if we come into contact with them again, our immune system knows what to do. The vaccine gives us immunity, so we don't get sick or so our illness is much milder than it otherwise would have been.

There are four categories of vaccines in clinical trials: whole virus, protein subunit, viral vector and nucleic acid (RNA and DNA). Some of them try to smuggle the antigen into the body, others use the body's own cells to make the viral antigen. All of them are trying to achieve the same thing – immunity to the virus, and some might also be able to stop transmission. They do so by stimulating an immune response to an antigen, a molecule found on the virus. In the case of COVID-19, the antigen is typically the characteristic spike protein found on the surface of the virus, which it normally uses to help it invade human cells.

Many conventional vaccines use whole viruses to trigger an immune response. There are two main approaches. Live attenuated vaccines use a weakened form of the virus that can still replicate

without causing illness. Inactivated vaccines use viruses whose genetic material has been destroyed so they cannot replicate, but can still trigger an immune response. Both types use well-established technology and pathways for regulatory approval, but live attenuated ones may risk causing disease in people with weak immune systems. Inactivated virus vaccines can be given to people with compromised immune systems. Covaxin (code named as BBV152) is an inactivated virus-based COVID-19 vaccine developed by Bharat Biotech in collaboration with the Indian Council of Medical Research -National Institute of Virology.

Subunit vaccines (Fig. 13) use pieces of the pathogen - often fragments of protein - to trigger an immune response. This type of COVID-19 vaccine contains harmless S proteins. Once our immune system recognises the S proteins it creates antibodies and defensive white blood cells. Doing so minimises the risk of side effects, but it also means the immune response may be weaker. This is why they often require adjuvants, to help boost the immune response. Adjuvants are substances formulated as part of a vaccine to boost immune responses and enhance a vaccine's effectiveness.

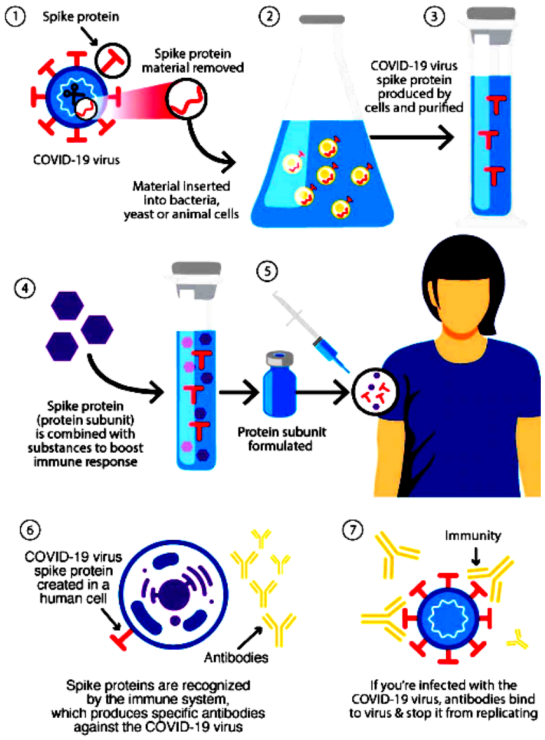

Fig. 13: *Protein subunit vaccine (Courtesy: Mayo Foundation for medical Education and Research)*

Messenger RNA (mRNA) vaccine (Fig. 14) is a type of vaccine uses genetically engineered mRNA to give our cells instructions for how to make the S protein found on the surface of the COVID-19 virus. After vaccination, your immune cells begin making the S protein pieces and displaying them on cell surfaces. This causes our body to create antibodies. If we later become infected with the COVID-19 virus, these antibodies will fight against the virus. The Pfizer vaccine (BioNTech COVID-19 Vaccine) uses messenger RNA (mRNA). This is what carries the instructions for making the "spike" protein that lets the virus enter human cells. The mRNA vaccine tells our immune cells to make the protein and act as if they've already been infected with the coronavirus, giving us some immunity against it.

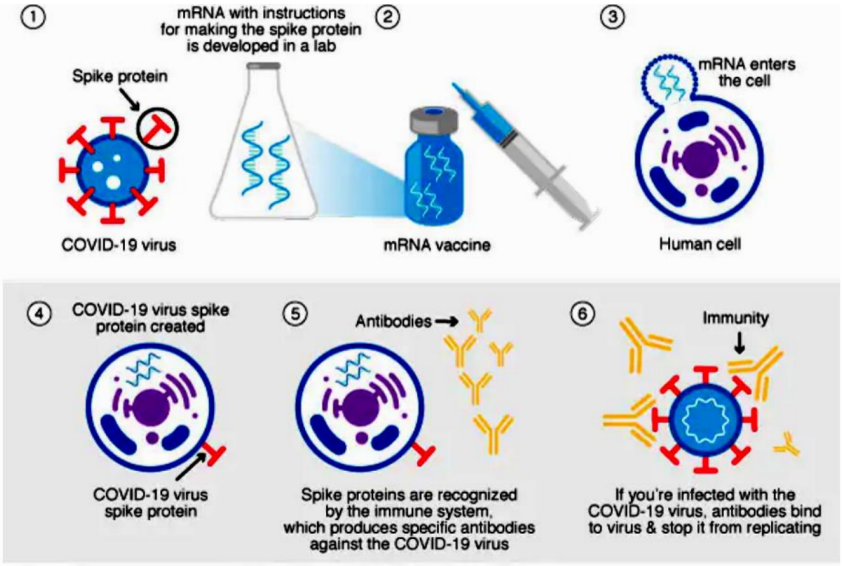

Fig. 14: *mRNA vaccine (Courtesy: Mayo Foundation for medical Education and Research)*

Vector vaccine is a type of vaccine, genetic material from the COVID-19 virus is placed in a modified version of a different virus (viral vector). When the viral vector gets into our cells, it delivers genetic material from the COVID-19 virus that gives our cells instructions to make copies of the S protein. Once our cells display the S proteins on their surfaces, our immune system responds by creating antibodies and defensive white blood cells. If we later become infected with the COVID-19 virus, the antibodies will fight the virus.

Viral vector vaccines (Fig. 15) can not cause you to become infected with the COVID-19 virus or the viral vector virus. Also, the genetic material that's delivered doesn't become part of our DNA. The Janssen/Johnson & Johnson COVID-19 vaccine is a vector vaccine. AstraZeneca and the University of Oxford also have a vector COVID-19 vaccine.

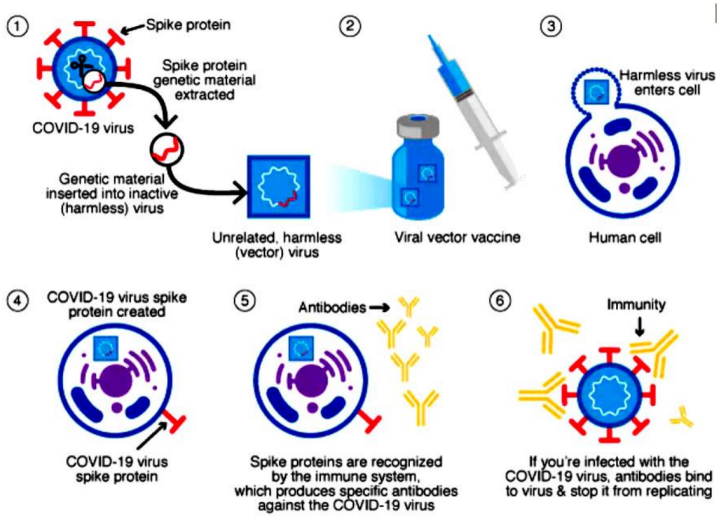

Fig. 15: *Viral vector vaccine (Courtesy: Mayo Foundation for medical Education and Research)*

In India three vaccines were approved for vaccination for example Covaxin, Covisheild and Sputnik V. The CoviShield COVID-19 (AZD1222) (C19VAZ) vaccine, formerly known as ChAdOx1 nCoV-19, is made from a virus (ChAdOx1), a weakened version of a common cold virus

(adenovirus). In addition, genetic material has been added to the ChAdOx1 construct, which is used to make proteins from the SARS-CoV-2 coronavirus called Spike glycoprotein (S). On February 15, 2021, the World Health Organization (WHO) recommended the Serum Institute of India Pvt Ltd COVID-19 Vaccine (ChAdOx1-S [recombinant]) known as COVISHIELD. This vaccine was co-developed by AstraZeneca Plc and the University of Oxford on January 1, 2021.

In May 2020, Indian Council of Medical Research's (ICMR's) National Institute of Virology approved and provided the virus strains for developing a fully indigenous COVID-19 vaccine (Covaxin). In June 2020, the company received permission to conduct Phase I and Phase II human trials of a developmental COVID-19 vaccine. In November 2020, Covaxin received the approval to conduct Phase III human trials after completion of Phase I and II.

The Russian COVID-19 vaccine Sputnik V (Gam-COVID-Vac) is an adenoviral-based, two-part vaccine against the SARS-CoV-2 coronavirus. Initially produced in Russia, Sputnik V uses a weakened virus to deliver small parts of a pathogen and stimulate an immune response.
The Sputnik V (Gam-COVID-Vac) vaccine reduces the time taken for the actual development of immunity to SARS-CoV-2, the betacoronavirus behind the COVID-19 pandemic.

It is a vector vaccine based on adenovirus DNA, in which the SARS-CoV-2 coronavirus gene is integrated. Adenovirus is used as a "container" to deliver the coronavirus gene to cells and start synthesizing the new coronavirus's envelope proteins, "introducing" the immune system to a potential enemy. The cells will use the gene to produce the spike protein. The person's immune system will treat this spike protein as foreign and produce natural defences, antibodies, and T cells, against this protein.

The CDC also says the vaccines are safe for pregnant women and there is no indication they pose any danger to the fetus. There have been reports of adverse allergic reactions to some of the vaccines, so at present time; people who have a history of severe allergies are advised not to get vaccinated.

9. Post-COVID Complicacy

Although most people with COVID-19 get better within weeks of illness, some people experience a range of new or ongoing symptoms that can last weeks or months after first being infected with the virus that causes COVID-19. Unlike some of the other types of post-COVID conditions that tend only to occur in people who have had severe illness, these symptoms can happen to anyone who has had COVID-19, even if the illness was mild, or if they had no initial symptoms. People commonly report experiencing different combinations of the following symptoms:

- Difficulty breathing or shortness of breath
- Tiredness or fatigue
- Symptoms that get worse after physical or mental activities (also known as post-exertional malaise)
- Difficulty thinking or concentrating (sometimes referred to as “brain fog”)
- Cough
- Chest or stomach pain
- Headache
- Fast-beating or pounding heart (also known as heart palpitations)
- Joint or muscle pain
- Pins-and-needles feeling
- Diarrhoea
- Sleep problems
- Fever
- Dizziness on standing (light-headedness)
- Rash
- Mood changes
- Change in smell or taste
- Changes in menstrual period cycles

10. Conclusion

The COVID-19 pandemic has affected the world in various ways. This new virus outbreak has challenged the economic, medical and public health infrastructure of the world. Time alone will tell us how we conquer the virus. Although, the severity of the virus has been reduced little bit, still its outburst is continuing. This pandemic needs the cooperation and awareness of entire populations to reduce the spread of the disease. The government should develop effective strategies and give topmost priority to prevent the outbreaks of virus. During COVID-19 pandemic and long term lockdown period, many people have lost their job. In general overall economic condition touched the sediment. So, at the same time, it is also important that government should try to improve the economic condition of the people of their own country.

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