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Review Article

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COVID-19 (CORONA VIRUS DISEASE-2019)

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INTRODUCTION

The world has been battling Coronavirus since months. Since the first case originated in late 2019 In the city of Wuhan, China. The virus has made its way across the globe causing economic decline, quarantine and death. The World Health Organisation has officially raised the Global alert to the highest possible level. This Novel Corona Virus is a cause for global concern because how little we know about it and how quickly it is spreading. Tait-Burkard, associated Professor at the Roslin Institute of Edinburgh, said that what makes this Novel Coronavirus Unique is that it is much severe than SARS and MERS viruses, it also means that a lot of people remain undetected as its looks like a normal common cold and they don't develop very severe symptoms and infected people are already sharing the virus while they look health.

Now firstly, the Novel Coronavirus has been named as **SARS – CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus-2)**, while the disease it causes is called **COVID 19** short for **"Coronavirus disease 2019" [Fig :1]**. As of now, the WHO estimates that the death rate of COVID–19 is around 3.4%, which is higher than the Flu (< 0.1%). SARS-CoV-2 has so far infected less than a flu has, and estimation between the two change as time moves on. However, in the comparison now, it is still evident that lives are its stake from COVID-19 which is why scientists are working vigorously on understanding its transmission, behaviour and how they can stop it.

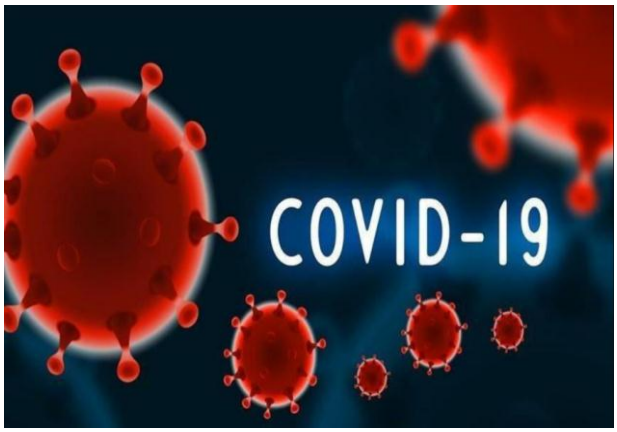

Fig. 1: Image of Covid- 19 (Image source- reference 1).

Since, this disease is a pandemic, what we have learned about it and how fearful should we be?

Coronavirus is a family of viruses which are named for their structural elements. They have this very prominent protein on their surface called **"Spike protein"**, we can see them very prominently in the microscope. The viruses which belonging to this family are known to cause Pneumonia like symptoms. In most cases Coronaviruses are respiratory RNA virus which affects animals such as Bats, Cats and Birds. But when they make a jump to Humans these viruses are known as Zoonotic. There are 7 known Coronaviruses causing infection to humans, they are

1. 229E (alpha coronavirus)
2. NL63 (alpha coronavirus)
3. OC43 (beta coronavirus)
4. HKU1 (beta coronavirus)
5. MERS-CoV (beta coronavirus that causes Middle East Respiratory Syndrome or MERS)
6. SARS-CoV (beta coronavirus that causes Severe Acute Respiratory Syndrome or SARS)
7. SARS-CoV-2 (the novel coronavirus that causes Coronavirus Disease 2019 or COVID-19)

SARS and MERS are previous known outbreaks from the last few decades. In 2002 there was SARS outbreak and in 2012 there was MERS outbreak. The each took less than 1000 lives, but both are known to cause severe causes of pneumonia and lung injury. Death rate of these infections are higher than COVID-19 from 11% to more than 30%. So, what we see with this virus is that it is much milder than SARS and MERS. In fact, mortality rates from COVID-19 vary on age and previous health of the patients. Since it is not the Coronavirus itself, but how your immune system responds. For any viruses to cause a human disease they need to get into human cells, different viruses like to grow in different cells of the body. This new coronavirus likes to grow in lung cell. The spike protein which is present on the surface of the

SARS-CoV-2 binds to a specific protein in the cell wall like lock and key mechanism, which directs the cell to take off this virus so that it can eventually hijack the cell machinery and use it to make more of its replica. This virus binds to a protein called ACE2 (Angiotensin-Converting Enzyme 2) present in the host's cell wall which is a receptor. So, the virus has to bind with the receptor to be able to get inside the cells. ACE2 is found throughout the respiratory tract and SARS-CoV-2 likes the cells of both upper and lower part of our respiratory system. The lower respiratory tract includes trachea, bronchi, bronchioles and alveoli. The upper respiratory tract includes the nostrils, nasal cavity, mouth, throat, and voice box. When we have an infection in our lungs, a lot of immune cells accumulate in the infected region to defeat the virus. The infected cells can no more take oxygen and because of the damage there is an accumulation of fluid in the infected part of the lung and that's what is called pneumonia. Most of the COVID-19 patients have died because of pneumonia. The other symptoms of this disease include fever, tiredness, and dry cough. Some people may also experience aches and pains, nasal congestion, runny nose, sore throat and diarrhoea. 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. Some people may also remain asymptomatic and continue to spread the virus. There are other factors that can make this disease a lethal disease. According to the data available, it seems that most of the people died because of this COVID-19 disease so far were either elderly or they had underlying disease condition. If our immune system is compromised for some reason, then we have higher chances of getting severe infection.

To understand the origin of SARS-CoV-2 and its transmission, scientists sampled its genomes in 53 individuals back in January 2020. They converted the viruses' nearly 29000 nucleotide bases into workable DNA, which was shared with Labs across the globe. Based on the DNA they were able to distinguish that the Virus was roughly 96.2% similar to a Bat Coronavirus and 79.5% similar to SARS-CoV. SARS-CoV-2 seems to have started in bats but there need to be a link between how the coronavirus lived in bats is slightly different to the coronavirus which leaves in humans and the link is still unknown. Despite the early theories that COVID-19 disease originated in seafood market in Wuhan, there is evidence that it might not be the case. As per February 2020, teams in China and US's National Institute of Allergy and Infectious disease are already testing an antiviral drug called Remdesivir to combat the spread. Created by US based Biotech company named Giliet, the experimental drug was shown to block the activity of a protein that helps coronavirus to make copies of themselves. Lab tests showed promises for animal models like SARS and MERS and the treatment was also successful when used on a US patient with COVID-19 infection. While the FDA has not approved this drug, clinical trials has started with 270 patients at Beijing's China-Japan friendship hospital, roughly 1000 patients spread throughout Asia and US has also administered similar treatment.

A lot of future efforts are going to be focusing on drug development because it is very clear right now that these viruses might continue to jump from animals to humans, so we should be ready to face another outbreak in the future and the antiviral drug and vaccine development are way to go.[2,3,4,38]

Structure of SARS-CoV-2

Viruses are essentially protein packages surrounding genetic material. They cannot survive without a host and it is debatable whether they are living or non-living. The structure of viruses and other microbes help us to understand their various properties like how they survive, how they infect and also help us to deduce methods for detecting them and also develop ways to prevent and treat the infection. Viruses can only survive within a host cell. Viruses have a genetic material which enables them to reproduce, however they do not have enzymes required for protein as well as nucleic acid synthesis. So, they require a host cell so that they use their machinery and produce proteins and enzymes necessary for their production as well as for their multiplication.

Basic structure of virus:

All viruses have a genome which is surrounded by a protein coat known as capsid which are arranged in a symmetrical manner to form a protective shell for the nucleic acid. The symmetry maybe either icosahedral (i.e. has 20 triangular faces) or helical. Some viruses maybe enveloped, or some may not be enveloped (naked viruses) [Fig 2]. The envelope is made up of lipoproteins (lipids and proteins). The lipids are derived from the host cell membrane which the virus infect, and they acquire it while they are leaving the cell and the proteins are synthesised by the viral genome using the host cell machinery.

Viruses have been broadly classified into 6 types based on their genome,

1. 1st class includes viruses with double stranded DNA.
2. 2nd class includes viruses with single stranded DNA.
3. 3rd class includes viruses with double stranded RNA.
4. 4th, 5th and 6th class are single stranded RNA viruses with some difference,
5. 4th class includes viruses with positive strand, single stranded RNA i.e. RNA same as that of mRNA which can be directly translated into proteins.
6. 5th class includes single stranded RNA viruses with RNA of opposite polarity to that of mRNA are present i.e. negative stranded RNA.
7. In 6th class, single stranded RNA viruses are included in this class, but these viruses have the capability to synthesise DNA from their RNA using an enzyme called Reverse Transcriptase.

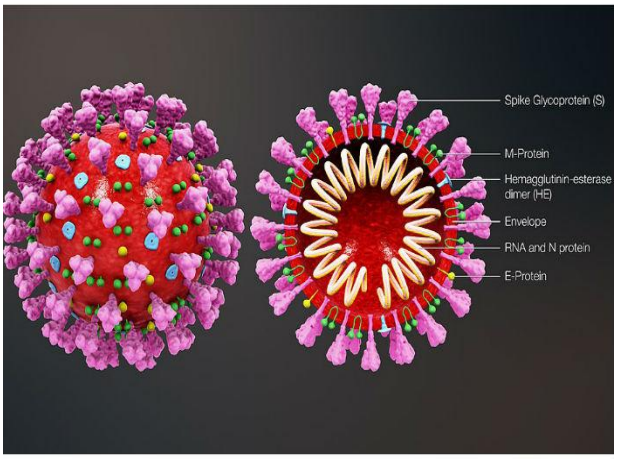

Fig. 2: Structure of SARS-CoV-2.[5]

Coronaviruses belong to **4th class i.e. they have single stranded positive sense RNA with a protein coat**. Coronavirus genome is very large in fact it is among the largest mature RNA virus molecules known and second the nucleocapsid has helical symmetry. Also, Coronaviruses are enveloped viruses i.e. apart from the protein coat, they also have lipoprotein envelope. The lipoprotein envelope has lipids derived from the host cell membrane and the protein in this envelope are synthesised from the viral genome. One of these proteins known as **'Spike protein'** forms a kind of rim out around the membrane. The rim gives it an appearance similar to corona of the Sun and that's why this virus is named as Coronavirus. Presence of this Spike protein is the characteristic feature of Coronavirus. This spike protein is the one through which the virus attaches to a receptor and then the viral membrane fuses with the host cell membrane causing the viral genome to enter the cell.

The spike protein is also called **S protein**. The spike protein is less triangular and roughly cylindrical in shape. This protein is heavily glycosylated. During replication it uses our body's own enzymes to covalently attach sugars to the genes near protein surface. This glycosylase protects the virus from our immune system. The spike protein is made up of three intertwined chains that have identical amino acid sequences.

There is a "receptor binding domain (RBD)" in the spike protein which is critical to the viral life cycle. The RBD is where this virus binds to an enzyme on the host cell's surface enabling it to fuse with the cell and transport viral genetic material inside the host cell. Two of these RBD's are in down conformation in its structure, however one of these RBD is flipped up. This up conformation is higher energy designed to bind to cellular receptor and result in fusion. When the spike protein binds each of the RBD, it shifts into less stable up conformation. Our own peptide bond breaking enzymes called proteases can cut the spike protein at specific sites and conformational changes in the spike protein enable fusion to occur.[6]

A different research group published a crystal structure of just the RBD of spike protein. It showed that the RBD binds to **Angiotensin-converting enzyme-2** also called **ACE2** which is a receptor in our cell surface to which Coronavirus binds to cause fusion. These structures are heavily glycosylated. There is an extensive Hydrogen bonding network at the RBD-ACE2 interphase involving two Tyrosine (Tyr) residues [Tyr-489 from RBD and Tyr-83 from ACE2]. The tyrosine side chain is also hydrogen bonded to the carbon of Asparagine (Asn-487) side chain of RBD and this intern bonds to the carbon of Glutamine (Gln-24) of ACE2 through its N-H bond's hydrogen atom. Moving along the ACE2 α-helix, we have a Glutamic acid side chain (Glu-35) and a Lysine residue (Lys-31) which carries a positive charge. These residues are both involved in hydrogen bonding with Glutamine (Gln-493) sidechain. This H-bonding is relatively short. There is another where there is extensive H-bonding, some between amino acid backbone atoms and some additional hydrogen bonds among polar charged residues. Overall characterisation of spike protein is super important because this paves the way for vaccine development. If we introduce small harmless peptides that resemble the spike protein our immune system can recognize and build up antibodies against it and thus protecting us from COVID-19 infection in the future. Also knowing to what RBD binds to could help us develop treatments that tie up the virus by binding it outside of the cell before it's able to fuse and cause infection.[7]

In addition to spike protein there are two other proteins, one is known as **Membrane protein** or **M protein** which gives the virus envelope its shape and the other one is **Envelope protein** or **E protein**. They have roles in the assembly of the virus genome, capsid and the envelope as the virus leaves the host cell.

If the virus undergoes fusion, the viral genetic material is injected into the cell. In case of coronaviruses this piece of RNA travels to our own ribosome and Hijack them to create its own viral proteins. Viral translation using our ribosomes makes the proteins that the virus needs to assemble the additional copies of itself which will eventually be released from the cell and they are called as **virions.** These virions infect other cells. SARS-CoV-2 protease is a dimer made up of two identical protein chains and it must dimerise to become a functional protease. The iconic interaction between the two amino acids called Arginine (Arg-4) and Glutamine (Glu-290) drive the dimerization.[8]

How long does the Novel Coronavirus live on surfaces?

Let us address how long a virus can linger on surfaces and what we should be wiping down to keep our self and others safe as much as possible. First of all, the scientific literature on this subject is very limited. The novel coronavirus is just as it means, New. So, some of this information is still in the preprint phase and maybe

changed. But this information is much more vigorously tested than the information flying in the social media. One study from the National Institutes of Health in US examined how long can the coronavirus that causes COVID-19 can remain viable on a few common **"fomites"** or materials that can transmit infections. The fomites that were tested include copper, stainless steel, cardboard and one of the most common plastics called polypropylene, which is used to package food and it also exists in our kitchen.

The researchers found copper was the toughest for the virus to survive, 4 hours after exposure they couldn't find any that were viable or capable of infecting a person. Cardboard was the next toughest for the virus with none found viable after 24 hours. Stainless steel and plastic were much more accommodating with viable examples detected even after 72 hours of exposure. Just because there were viable viruses that doesn't mean their concentration was dropping. In fact, their concentration dropped a bit and it did so faster on stainless steel than in plastic. That is because more viruses degrade out of their living host. So, one may not get infected by contacting contaminated surface days after the virus was deposited there, it is not as risky as contacting the contaminated surface within few hours after contamination [Fig 3].

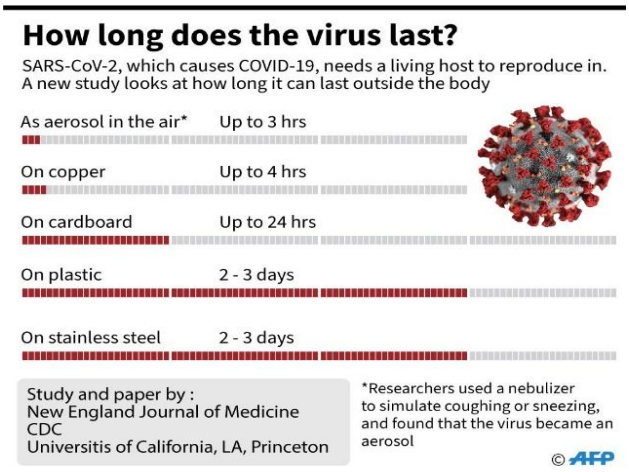

Fig. 3: Information regarding virus last on different surfaces.[9]

The study also examined how long the virus was viable while suspended in aerosols. The experiment lasted three hours and the virus remained viable in entire time with not much concentration. But that doesn't mean that the virus is airborne. The researchers aerosolised the virus artificially by spraying it into a mist and keeping it inside a special rotating drum. In contrast when an infected person exhales or coughs, the virus is typically carried in larger droplets which don't stay suspended in the air for a long time. If the droplets land on a person then it is a problem. These are the results from tightly controlled laboratories. In the real world it is possible that UV light from the sun disinfects the contaminated surfaces faster. It is also possible that even in the packages that were transferred over 24 hours was just sneezed before it was left on the door.

Hopefully what this information makes you clear that why you are asked to wash your hands frequently and avoid touching your face while going out. SARS-CoV-2 spreads most effectively from person to person, so if you touch surfaces which can be contaminated avoid touching your face because it may infect you through mouth, nose and eyes. Washing your hands with soaps destroys virus effectively and as a bonus soap also envelops fragments of virus and carry them away. This makes soap more effective than hand sanitisers. Hand sanitisers and alcohol wipes are more effective if they contain more than 60% alcohol in them. So, you should wipe down frequently touched surfaces like doorknobs, switchboards, and remotes. One should also not miss to wipe mobile phones which frequently touches hands and face. Most importantly don't panic and at a time like this good information saves life.[10,11,12,38]

Origin of SARS-CoV-2

So far, we know that the outbreak originated in the city of Wuhan, China. But as of now how the outbreak began has not been solved. We have heard seafood, snakes and a whole lot of conspiracy theories surrounding the virus origin. But it seems that preliminary evidence is pointing all to a familiar source, Bat [Fig 4].

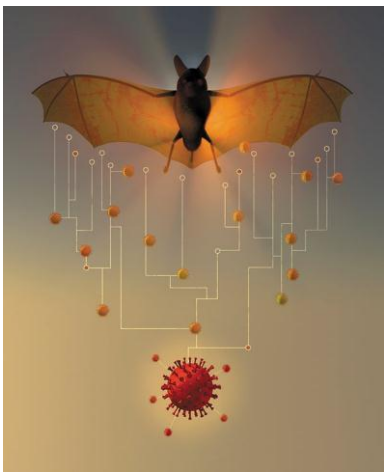

Fig. 4: Evidence is pointing all to a familiar source, Bat.[13]

When scientists looked at the genetic sequence of the virus, they could match it with every other known coronavirus. There is one particular Coronavirus that was found in China which was isolated from the Bats and this Bat Coronavirus was similar to SARS-CoV-2. SARS-CoV-2 has 96.4% similar genetic sequence to that of Bat Coronavirus. And this is not the first time that Bats have been identified as potential source of the outbreak, in fact studies have found that Bats host a larger proportion of zoonotic virus than any other mammal which makes them the disease reservoirs. Viruses which cause Ebola, SARS-CoV and MERS-CoV is also zoonotic, meaning they can cross from animals to Humans. To better

understand these zoonotic viruses a team in Southern China has worked on more than 10,000 Bats and they significantly discovered more than 5000 new Coronavirus in past 10 years.

Now to eventually understand how the SARS-CoV-2 can potentially cross between species researchers are looking at it on a cellular level. When scientists found the Coronavirus in Bats, they recognised the spike protein in its surface and they studied how they can bind to Human cell surface receptors, eventually hijacking the cell. So how exactly can Bats harbour all these viruses and not be affected? The answer could be in how Bats evolved to fly. Bats are the only mammal capable of flying long distances and it uses tremendous amount of energy to do so. But a by-product of this high energy demands is believed to be an increased number of free radicals in their cell, which in turn can damage the Bat's DNA. So, to overcome these harmful effects it seems that Bats have evolved genes to strengthen their immune response, so that they don't react to free radical damage caused by flight. Bats have unique adaptation in their immune system which allows them to harbour these viruses without causing any disease. So, Bats may not get sick but when the viruses make jump from species to species with the same immune strength, like say to Humans the mortality rates can be high. Environmental threats like deforestation could act on the animal's stress level, causing them to shed viruses through their saliva, urine and faeces which can later infect other mammals.

Bats maybe the host for many viruses, but we cannot forget their crucial role in regulating insect population and as important pollinators. With many plants depending on them for their survival, they are also an important part of our ecosystem.[14,15,16,38]

Face masks at the time of a pandemic

How useful are face mask during Coronavirus crisis? Experts can't really agree on this. Should we wear them? If so, who should wear them? Does wearing mask protect the wearer or does it protect the other person? And which type of mask makes sense at all? In many Asian countries face masks are regarded as a major weapon to fight COVID-19.

We can generally distinguish masks into three main types. So called Filtering Face Piece masks or FFP masks fits perfectly around the nose, mouth and chin and they filter out tiniest particle. They let no viruses in or out. An exhalation valve makes breathing more easier, but it increases the risk of escaping of viruses. So, an unvalved mask protects both the wearer and the person they encounter. N95 mask or N95 respirator is a particulate filtering face piece respirator. It filters at least 95% of airborne particles. It is an example of a mechanical filter respirator, which provides protection against particulates (air borne particles) but not against gases or vapour. FFP masks and N95 masks are short in supply worldwide. So, they should be mainly reserved for medical personals and infected patients. A mask that's often seen nowadays is a simple protective face piece for the mouth and nose called surgical mask. It consists of several layers of paper or non-woven fabric and a thin wire to make it fit over the nose. When the wearer coughs or sneezes, the surgical mask block the large droplets. But on inhalation, air also flows by the sides. So, the surgical mask protects others from the infection rather than the wearer. Once the mask is wet from breathing after 8hours of wearing time at the most it must be discarded [Fig 5].

Fig. 5; Types of masks.[17]

In COVID-19 crisis, manufactured masks are in short supply. That has led to a flourishing cottage industry to stitch cloth masks. A textile mask functions rather like a protective mask made of paper and it blocks only 1/3rd of the droplets as that of a surgical mask does. However, a cloth mask can be washed and reused. The literature on how well different homemade masks block particles or aerosols or droplets from both coming in and going out is still unclear. So, teams of scientists are now informally trying to determine how good certain materials are at blocking droplets or particles and are sharing their research publicly. The key is to find a material or combination of materials that blocks particles but one can still breath through.

One team from Jeremy Howard, a University at San Francisco tested different kind of air filters, like furnace filters and said when these filters are added in two layers their filtering efficacy was about 94% and in six layers the efficacy was 95%. But these filters are not safe to be worn directly next to our face, as they could shed particles that are harmful to breath. So, a filter like this should be sandwiched between two layers of fabric. This group also tested some common fabrics. Four layers of 600 thread count sheet filtered out 60% of microparticles, two layers of thick woollen scarf filtered out 48.8% of microparticles, three layers of coffee filters filtered out 50% but turned out to be less breathable and a cotton bandana by itself only filtered out 19.5% even when four layered.

Another study indicated that high thread count cotton in a double layer could perform almost like a surgical mask and they also cautioned that homemade masks using a less thick fabric has filtration rate less than 1%. So, materials must be chosen wisely. These results has not been previewed or published and it is also necessary to

mention that the filtration rates mentioned are from highly controlled laboratories that tested just the materials by themselves and didn't test the protection for actual Coronavirus but for particles of that size. When worn in a mask form depends on if one is wearing the mask properly. Importantly, one should remember that reducing the risk of infection mainly depends on not touching your mask and face with unwashed hands. Masks can give you a full sense of security, but social distancing and hand washing are number one tactics for slowing this pandemic. No matter which mask you wear it can only be effective if you implement hygiene measures like hand washing and social distancing.[18,19,20,38]

Diagnosis of COVID-19

As the COVID-19 infection spread around the globe, WHO asked all countries to act quickly. There are two important tests for COVID-19, one that can confirm if you are currently infected (RT-PCR test) and another that can tell you if you are immune (antibody test), both are critical for collective recovery. After pneumonia cases started to rise in Wuhan, researchers in China worked quickly to identify the virus, sequence it and publish its genome immediately. Shortly after a team in Germany designed the world's first COVID-19 diagnostic test which is Polymerase Chain Reaction (PCR) test [Fig 6,7].

Fig. 6: Antibody Test.[21]

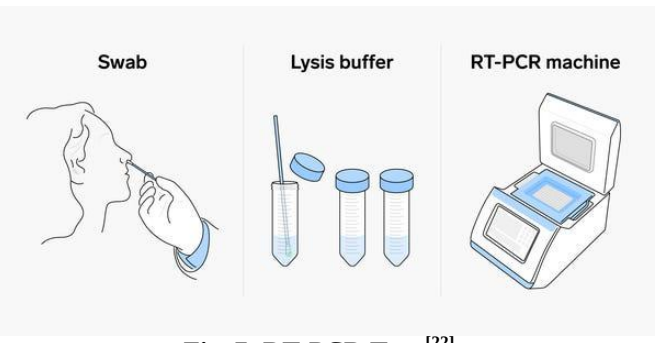

Fig. 7: RT-PCR Test.[22]

It is a standard molecular biology technique that scientists are using for decades. To find out whether one is infected by this virus, the doctor will give him/her a RT-PCR test (Reverse Transcriptase-Polymerase Chain Reaction test). It a molecular photocopying technique that can detect the presence of a virus's genetic material in a sample. Since SARS-CoV-2 is a single stranded RNA virus, a RT-PCR test uses chemicals and special enzymes to convert that RNA into DNA and then make billions of copies of it to confirm if there is an infection. It all starts with a Nasopharyngeal swab which is inverted through the nose and pushed all the way back to the sinuses. All the mucus and cells from that swab are broken up. Then the RNA is extracted, then that extracted RNA is transferred into DNA using an enzyme called reverse transcriptase as the PCR test requires DNA. Once we have that DNA made from the swab then PCR is done. The viral DNA thus obtained is broken and that bits of DNA that binds to that viral DNA is added and polymerase chain reaction takes place as a result of which more copies are made only if they are present. If the viral DNA is present the PCR reaction will then amplify the viral DNA and it is a positive test. The WHO published the protocols for the German team's PCR test and distributed it worldwide. This PCR test is important for detecting current infection but only for a specific period of time. Because once a patient starts recovering his immune system will clear out the viruses.

In such case there is another test called antibody test, it is also called serological test and it looks for the presence of antibodies in the blood sample. This would help the experts to track the full scale and the spread of the virus and also confirm who ever is immune. The antibody test uses a diagnostic technique called ELISA (Enzyme-Linked Immunosorbent Assay). This test uses a plate inside which are wells within which there are tiny pieces of virus. So, when a patient's blood is added and if any Coronavirus fighting antibody is there it will bind to those pieces. Specialized enzymes and substrates are then added, which changes the colour of the well if antibodies are present. This is an important test that could find asymptomatic carriers, clarifies who is safe to work on the front lines, help for future treatment and could be a key indicator for when we can re-enter the society. But this test is not a quick fix, we don't know yet if testing positive for antibodies means a patient is fully immune to the virus. Researchers are moving fast here, but there is only been so much time to study COVID-19.[23,24,25,38]

Treatment modalities: Antiviral drugs are medications used to treat viral infections. Antiviral inhibits a virus's ability to duplicate, this also means they are most effective when administered shortly after infection, that is before the virus has infected too many of the host cells. Unlike vaccines which serve out immunity by training our body's immune system to fight pathogens. Antivirals are administered to people who are already infected with the virus. Another key difference is antivirals are effective only at that time when they are administered, so essentially antivirals are an effective near-term solution to prevent viral infections from getting worse. But the action of vaccine stays effective

throughout the life once after administration. It means, if you have vaccine against a pathogen or an antigen you will not be infected by the same throughout your life, since your immunity is being trained to fight the same. Nearly since six decades when first antiviral drug has been approved for use, antivirals have been used to treat a number of viral infections including HSV, Chickenpox, Hepatitis etc. to name a few.

In January China shared the genomic sequence of SARS-CoV-2. Till now researchers have had only few months to study this virus. Fortunately, researchers can use other Coronaviruses which we are known to us like SARS-CoV and MERS-CoV to study this virus. Researchers believe that SARS-CoV-2 follows the same process of replication as other Coronaviruses do. Once the spike protein present in the surface of the Coronavirus binds to ACE-2 receptor of the Human cell, the virus fuses with the cell and releases a copy of its RNA genome. Then through transcription and translation it makes copies of itself. These copies of infectious particles are called the Virions. Finally, these virions are released to infect the adjacent cells. Different antiviral drugs are designed to target different steps in the process of viral replication. Some antivirals target receptors early in the process to stop fusion to the host cell, others stop replication of the genome and others disrupt the assembly of new copies or stop the release of virions. And when experts are saying it'll take more than a year for a vaccine to come into market, researchers worldwide are trying to find a near term solution in the form of an effective antiviral treatment. Instead of developing a new drug, specifically for COVID-19 which will take a decade to come into market, many are looking to repurpose antivirals that have already gone through vigorous trial and approval processes to treat other diseases. Two examples are antimalarial Chloroquine and its derivative Hydroxychloroquine [Fig 8], which is also used to treat Rheumatoid arthritis. Now, just to be clear there is currently no defendative evidence that either of these antivirals are effective treatment for COVID-19. Researchers still need to fully evaluate the efficacy of these drugs against COVID-19. But some researchers think these drugs could potentially stop SARS-CoV-2 by disrupting binding, by interfering in the process of depositing its genome into the host cell, stopping the virus early in replication. Chloroquine and Hydroxychloroquine also inhibit dangerous overreaction from the immune system.

Dr. Otto Yang, associate chief, Infectious Disease UCLA and his team are looking at another antiviral **Remdesivir**. This is an experimental antiviral that have been developed to treat Ebola, which inhibits viral replication by disrupting RNA transcription process. But there is a chance that it might also suppress the immune reaction and inflammatory response that has been a known cause of death for COVID-19.

There is also Favilavir [Fig:9], a drug that is used in Japan and China to treat Influenzas and it is currently being doubted as the first approved Coronavirus drug. The reality is there is no defendative evidence that any of these antivirals are effective treatments for COVID-19. So, for now there is no FDA approved drug, specifically for the treatment of COVID-19. The FDA has approved emergency use of Chloroquine and Hydroxychloroquine for the treatment of COVID-19. But in the same statement released on March 28th the FDA stated that Chloroquine phosphate and Hydroxychloroquine sulphate are not FDA approved for treatment of COVID-19. So, it is a little unclear that when and how these drugs can be administered, which makes the patient feel difficult to understand what therapies are available to them. Most researchers are exited about repurposing the antivirals to fight COVID-19, they need more time to confirm what dosage is most effective against SARS-CoV-2, they should also confirm what dosage is most effective and safe for public consumption. The pandemic has motivated and united the medical community to find an effective near-term treatment and many governments and companies around the world are fast tracking testing trials and approvals to find one.[28,29,30,38]

Fig. 8: Image of hydroxychloroquine drug.[26]

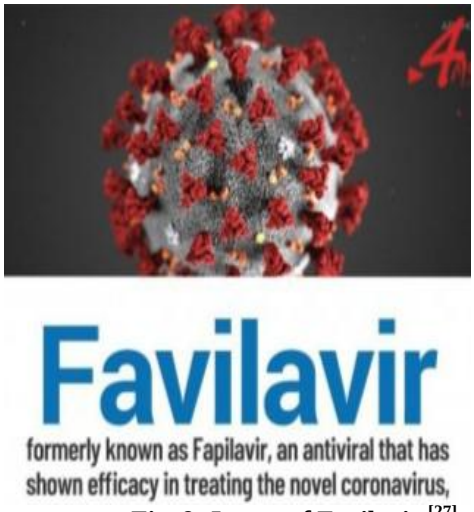

Fig. 9: Image of Favilavir.[27]

Plasma therapy

Blood Plasma

Discovered by German physiologist Emil von Behring, plasma therapy was first used in 1890. This therapy was used to treat diseases like Ebola, H1N1 etc. China, where Coronavirus outbreak first emerged, had used this treatment to treat critical COVID-19 patients. Two trials of plasma therapy were conducted on 15 patients having COVID-19 infection and they showed improvement. Several countries across the globe have started plasma therapy trials [Fig 11].

The process of donating plasma is similar to blood donation and takes about an hour. Plasma donors are hooked up to a small device that removes plasma while simultaneously returning RBCs. Plasma can be donated more frequently, as often as twice a week . The plasma drawn from one recovered person can help two infected people.

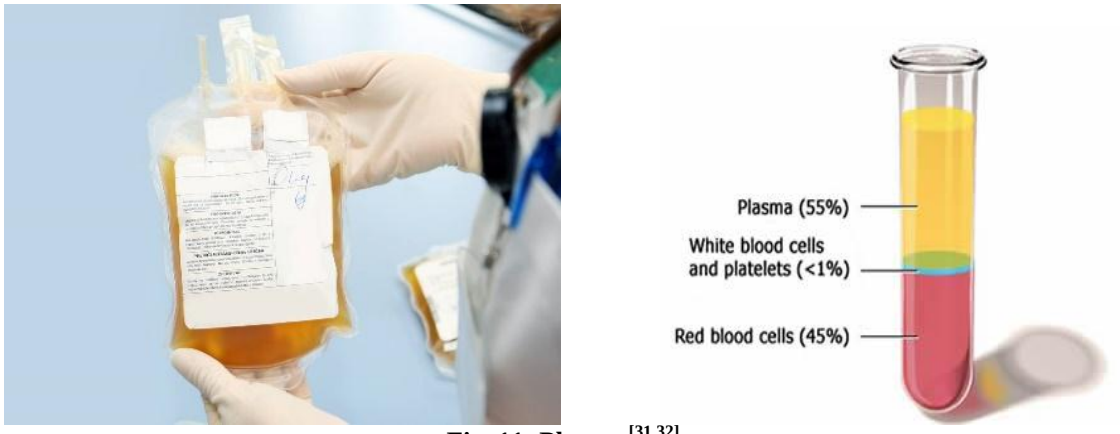

Fig. 11: Plasma.[31,32]

The idea behind this therapy is that immunity can be transferred from a healthy person to a sick patient using convalescent plasma. This therapy uses antibodies from the blood of a recovered COVID-19 patient, plasma to be particular about, and it is transfused to another COVID-19 infected patient. The recovered COVID-19 patient's blood would have developed antibodies to battle against SARS-CoV-2. Then plasma from the blood of this recovered patient is extracted and transfused to infected patient. Once the plasma of the recovered patient is infused into the blood of infected patient the antibodies present in that plasma will start fighting against SARS-CoV-2 in the infected patient.[33,38]

Vaccine for COVID-19

Researchers are working endlessly to produce a sustainable and reliable vaccine to finally end this crisis. There are teams globally working on vaccine solutions. As of 8th April 2020 there are 115 vaccine candidates in varying stages of research. Everyday there seems to be a new development. Private companies like Moderna and Inovio are making headlines as they are quickly progressing in the first stages of the vaccine approval process, a process that usually takes years is being pushed in a matter of months. That is the question, with urgency looming like this how viable are any of these fast vaccines, and is it possible that we will have a solution within next year?.

In under normal circumstances, taking vaccines from the lab to licencing for public distribution not only takes time but money. Roughly one billion dollars' worth or more. But a large part of the acceleration of the vaccines we are hearing about have to do with an international organization that launched in 2017, called "Coalition for Epidemic Preparedness Innovations" or "CEPI". CEPI gave the funds to organizations like Moderna, CureVac, Innovio pharmaceuticals and University of Queensland. And while funding helps to speed up the process, the teams chosen by CEPI are also already heading towards vaccine research. Teams already having experience in previous outbreaks like MERS are working on novel vaccine methods that could significantly reduce the development timeline, was selected for the development of vaccine for COVID-19.

Eventually a vaccine can be made in a few different ways. We have inactivated and live attenuated, both known as whole-pathogen vaccines, subunit vaccines including recombinant polysaccharide and conjugate vaccines which are using a piece of pathogen and the new method of nucleic acid vaccines using the DNA or the RNA of the pathogen. When injected into our bodies, vaccines aim to mimic the infectious agent. Typically, vaccines are given to boost the immune response. After the injection this response sounds the alarm in our body and begins the accumulation of WBCs like killer T cells and specific proteins called antibodies. Killer T cells destroy the pathogen in the infected cells and the antibodies neutralise the pathogen. In SARS-CoV-2's case the antibody will head towards the recognizable spike proteins on the outer shell and block the proteins from connecting to the receptors of our cells (ACE2).

This whole process of vaccination helps the immune system to get trained by the vaccine and retain the

memory of infection. So, when a vaccinated person encounters a real virus they can quickly recover. So basically, our body comes up with a preventive measure it needs to fight the pathogen, we just need to initiate the exposure.

Right now, CEPI has many funded candidates in their portfolio, out of those funded platforms we are hearing mostly four of them, two mRNA vaccine from Moderna and CureVac, one DNA vaccine from Inovio pharmaceuticals and a protein vaccine from Australia's University of Queensland/GlaxoSmithKline. Giving the urgency to find the vaccine during this pandemic, we are looking for new approaches like DNA and RNA vaccines because they can be developed quickly. However, that doesn't mean that work on other promising solutions stops. As experts are advocating various approaches when it comes to developing a vaccine, we also need many candidates as we have to pass the vigorous approval phases, but what exactly are these phases?.

For example, once a viable Coronavirus vaccine candidate has been identified in pre-clinical studies, then it can move on to the highly anticipated Phase 1 of the approval process. Phase1 studies involve tens of volunteers in batches. Moderna vaccine is being tested in US and it has reached phase1 approval involving 45 people. In phase1 approval process researchers find out whether this vaccine produce immune response in Humans and does it appear to be safe or not. Once the vaccine passes phase1 approval, it enters Phase2 which involves hundreds of volunteers. In this phase, the dosage, method of administration and quantity of vaccine is found out precisely, we might also get hints about effectiveness and researchers will also get a clear cut about the safety of using this vaccine. The distance between the phase2 and phase3 is called the "valley of death" and the reason for it is a vast majority of vaccines and drugs will not make it to pass phase2. And if the vaccine passes phase2 it passes to Phase3 where it involves more than 10,000 volunteers in a trial. In this phase researchers look for efficacy of the vaccine, that means researchers test weather the vaccine actually works by preventing the disease or it just create an immune response. Here the FDA collects all the data of the three phases and if all looks good, they will give the final approval of licencing and manufacturing of vaccine.

Researchers are looking at 12-18 months to effectively produce a viable vaccine by overlapping all the three phases. They may overlap phase2 to phase1 partially and see for better results and rather than waiting to get all the data to the very end of the trial, they may wait for a month for the best responses and based on those best responses the CEPI or government or company will ask to move on. But even if this ambitious timeline is accomplished, researchers will need to find the means of manufacturing it for 8 billion people on our planet. But if they overcome all these challenges, we'll be looking at a vaccine that was developed at a historical speed, one with a potential to save millions of lives.[35,36,37,38]

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