

Covid-19: Neither Cry Wolf Nor Stay Indifferent

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Abstract

Deriving its name from one of the membrane proteins that protrudes like a crown from the lipid membrane of virus, the **Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)** has been infecting human populations like wildfire across the entire globe transcending all barriers. Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR), the test widely used to detect its presence in humans, is carried out using the enzyme reverse transcriptase along with the polymerase chain reaction technique. Keeping in view the mountainous morbidity and mortality caused by the COVID-19 pandemic, efforts aimed at the development of a vaccine against it are proceeding on a war footing. With awareness to deal with the disease dawning gradually, isolation and social distancing remain the preventive measures to ward off this disease.

Keywords: Corona virus, COVID-19, CRISPR, Disease, Drugs, Pandemic, RT-PCR, SARS-CoV-2, Social distancing, vaccine

Introduction

A bunch of viruses appeared on the scene with a common structural feature; an extended crown like look, when they were observed under the microscope. The menacing group, christened as corona virus, has been found to be the cause of new human and animal diseases (Pal *et al.*, 2020). Beginning from the year 2003, many viruses were discovered one after the other. They were observed to be found responsible for diseases like SARS (Severe Acute Respiratory Syndrome) in the year 2003, along with MERS (Middle East Respiratory Syndrome) in the year 2012. To establish the virus-host relationship, many viruses were found in bats, some of them even caused diseases in human beings (To *et al.*, 2020). Seemingly, the virus causing COVID-19 has also mutated from one of the viruses thriving on bats (Zheng, 2020).

The COVID-19 virus measures 90 millimicron (mμ) and is 10 lac times smaller than that of a human host cell. The virus supports a small genome (genetic material) comprising merely around 30000 nucleotides intensely packed over a nucleocapsid protein scaffold, all enclosed within a lipid-protein membrane (Masters, 2006; Dömling and Gao, 2020). It is this lipid-protein membrane which breaks open, sounding the death knell of the dreaded virus,

when we apply soap to wash our hands thoroughly. Thus, hand washing with soap is an assured protection practice against this virus (Tuladhar *et al.*, 2015). The lipid-protein membrane has three proteins, most prominent being the protruding spike protein that gives the virus a crown like appearance and all familiar corona name (Laskar *et al.*, 2020). An illustration of structure and morphology of coronavirus has been given in figure 1 and 2. (Jameel, 2020; CDC, 2020)

The virus infects human beings mostly through the cells of respiratory tract and the interface between virus and human cells is through the spike protein of virus and human Angiotensin Converting Enzyme 2 (ACE2) and Transmembrane Serine Protease 2 (TMPRSS2). The cell surface proteolytic enzymes make virus enter the cell with virus getting into subcellular endosome through endosomal membrane fusion. Thereafter, begins the life cycle of virus and its multiplication inside the human cells with RNA and RdRp (RNA dependent RNA polymerase) getting multiplied along with 4 structural and 6 accessory proteins. Once multiple RdRp molecules are in place, a large crop of nascent virus particles results, of getting released from the infected cell (Nishiga *et al.*, 2020).

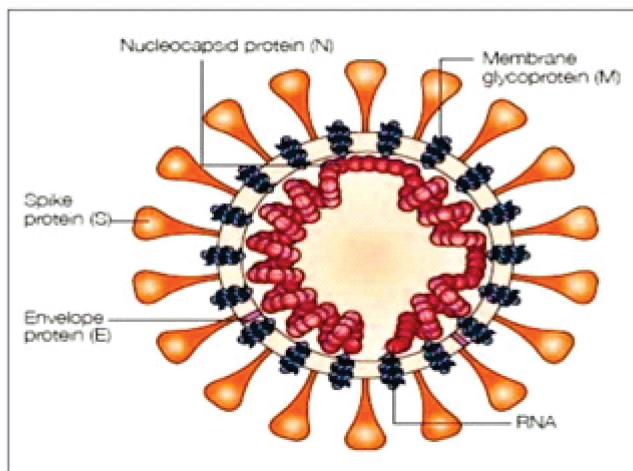


Fig. 1. An illustration of structure of coronavirus
(Source: Jameel, 2020)

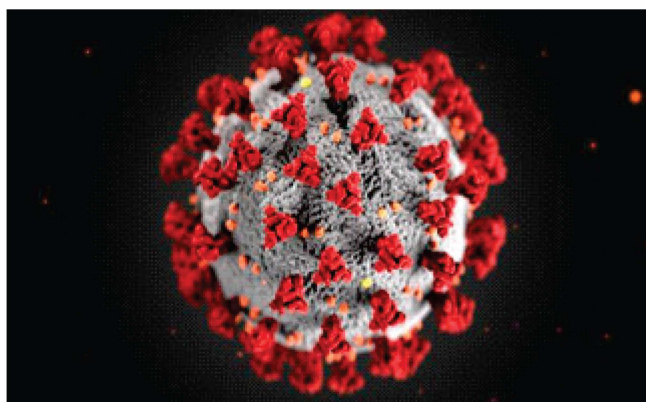


Fig. 2. An ultrastructural morphology of coronavirus
(Source: CDC, 2020)

Testing for COVID-19

Since viruses are very small entities, their detection to confirm the disease status is cumbersome. It involves the detection of the viral genome which is RNA in nature. The testing involves extraction of viral RNA, its enzymatic conversion into c-DNA which is scientifically known as reverse transcription. It is followed by multiplication of the miniscule c-DNA thus formed into a detectable mass. This is achieved by a technique known as Polymerase Chain Reaction (PCR). Due to the participation of Reverse Transcriptase enzyme along with application of PCR technique, the diagnostic procedure

is known as RT, PCR-Test (Reverse Transcriptase, Polymerase Chain Reaction-Test (Udugama *et al.*, 2020; Houlihan *et al.*, 2020). Discovery of this enzyme has won **Nobel Prize** to the researcher **HM Temin**, a US geneticist and virologist at the University of Wisconsin Madison, in 1975. The discovery also added a sensational aspect to the Centre Dogma of Molecular Biology about the synthesis of DNA from RNA (Dulbecco, 1995). The cDNA of virus is enmassed with the application of PCR reaction technique which was invented in the 1980s and again won **Noble Prize** for the US biochemist-**Kary Mullis** in the year 1993 (Hongbao, 2005). The PCR is an act of synthesizing innumerable number of COVID-19 viral c-DNA copies using a special high temperature resistant enzyme called Taq-polymerase. Such an enzyme is specifically necessitated because the polymerase chain reaction occurs at high temperature. This latter amazing enzyme is harvested from bacteria inhabiting hot Sulphur springs. The DNA formed from viral RNA and amplified profusely is quantified with the application of a fluorescent probe in comparison with +ve and -ve controls. Starting with RNA, all the steps from cDNA synthesis to the detection of amplified DNA are carried out through a servo equipment called PCR machine in an automated manner. It takes a few hours for the test. Multiple samples can be analyzed simultaneously (Lorenz, 2012).

Besides this, new testing methods, especially the simple ones, are being developed. Certain serological tests (viral protein as antigen and human response as antibodies) are also being developed to gain insight into epidemiological aspects of the disease. An interesting development towards detection is a paper-based test, named- **Feluda**- after a famous Indian fictional detective character created by Indian Bengali film director and writer- Satyajit Ray. It is based on the latest gene editing technology called **CRISPR** (Clustered Regularly Interspaced Short Palindromic Repeats) by Delhi based **CSIR- Institute of Genomics and Integrative Biology (IGIB)** with high sensitivity (96%), specificity (98%), low cost (Rs. 500) and quick results, within one hour as the hallmark (Pakrasi, 2020). Incidentally, **Emmanuelle Charpentier of France** and **Jennifer Doudna of U.S.** have shared this years (2020) Noble Prize in chemistry for developing CRISPR technique. Now seven women stood getting the Nobel Prize in Chemistry including the legendary Marie Curie (AlJazeera, 2020). CRISPR technique becomes a steppingstone towards finding a cure for inherited or genetically transmitted diseases and has implications towards Cancer cure and making of designer babies. **In essence, this pioneer women scientist duo has invented something epoch making, and they will be remembered as legends for this remarkable fait.** Normally, samples for COVID-19 detection are taken from

nose or throat as these are the favorite viral habitations and sample taking at these locations is least troublesome to the patient. Alternatively, samples for testing can also be taken from blood, sputum, and lung aspirates (Knoepfler, 2015; Dara and Talebzadeh, 2020).

COVID-19 Vaccines

A vaccine activates human body's immune system because antigenically, it is somewhat similar to disease causing microorganism (SARS-CoV-2 virus, in this case) but lacking in disease causing ability. In this way, the vaccine readies the body's immune system to identify and end the virus. There are ways galore to make the vaccines. To have a dead virus vaccine prepared, the virus is grown in a culture medium followed by its harvesting, purifying and chemical inactivation. The vaccine thus made is an injectable stuff such as Inactivated Polio Vaccine (IPV). In other ways, through genetic alterations or by repeated culturing, virus is made lame or attenuated as in the case of Oral Polio Vaccine (OPV). Another way in vogue to make the vaccine is through in vitro synthesis of certain viral proteins as in the case of hepatitis B virus (Okonek and Peters, 2020).

A bevy of vaccine candidates, the number running into 40s, are developed in different countries the world over, a few being mentioned below:

Serum Institute of India, Pune; one of the premier vaccines making company in the world, has tied up with Codagenix, a US based company to make the vaccine candidate. The concept involves the application of genetic engineering to produce an incapacitated form of virus capable of replicating at a snail's pace, eliciting an immune response, proving harmless to the host at the same time. China too is active in the field, working on a vaccine through the Sinovac company. It is formaline treated, attenuated form of virus and is expected to see the light of the day very soon in future.

In US, the elite-National Institute of Health has been working in collaboration with Moderna, a biotechnology company, on a new concept of vaccine making. Here, the information ingrained in the viral RNA is harnessed as mRNA to produce viral components sans virulence in the host, to create an immune response. The enthusiasm to make this vaccine runs so high that the ball is already set rolling on the phase I study to appraise immunoefficacy and safety of the vaccine in human subjects. Can anyone believe that the period between its development and clinical trials is a mere sixty days (Jameel, 2020).

In the US, Pfizer and Bio-Ntech too have worked on the same m-RNA (messenger RNA) technology. As the name suggests, m-RNA is a polynucleotide stretch where nucleotides are arranged in triplet codon to provide information for the sequence of amino acids in the

synthesis of protein by ribosomal machinery. A part of the viral RNA of COVID-19 coding for coat proteins is synthesized to act as m-RNA in this vaccine. When injected in the human being, it uses the cellular machinery to translate the genetic information into the viral protein. The human cells display this exogenous viral protein on their cell surface, and it is recognized as the antigen by the immune system to elicit a response by producing specific antibodies against it. The antibody army recognizes and combats the virus progeny as and when it infects the vaccinated person to begin the infection cycle. In this way the evil is nipped in the bud and the person is said to attain the immunity against the dreaded corona virus.

The vaccine is approved by the US FDA which, in the scientific world and medical profession, is the gold standard. The vaccines immunogenicity, safety and efficacy have been proven in the mandatory three phases of the trials. The limitations of this vaccine are the storage condition of -70°C to keep the mRNA intact as well as its high cost. This vaccine is also a tell-tale saga of a Hungary borne woman scientist, **Katalin Karikó**, who began working with this mRNA technology long ago. With little support or recognition, she kept working on this technology when she was a research student. When funding for her project ended in Hungary, she immigrated to Philadelphia in 1985. She worked like a lone crusader in quest of truth. She went ahead with her conviction, matching it with the courage of conviction. Her time of fame has come now with this vaccine technology seeming to produce the desired effect (Laczkó *et al.*, 2020 and Newey and Nuki, 2020).

Generally, vaccine making is tedious, multistep process where the laboratory product graduates to industrially manufactured entity confirming to all norms of safety and purity. Then follows the testing in animals and human beings. Even if the entire process is carried out at breakneck speed, it takes no less than two years for the validation of the vaccine as side effect free for humans (Iserson, 2020).

As time passes in the pandemic, better treatment options and survival chances are emerging for patients infected in September-October 2020 than those who got infected earlier in January-March 2020. Obviously, Doctors and Scientists understand more about COVID-19 now than that they knew 6-8 months earlier and thus, they can see patients in better light. Given hereunder are a few aspects of COVID-19 remedial measures which were hitherto elusive but came to the fore during July-October months:

- (a) Pneumonia, a lung infection of serious nature, was thought to cause death in COVID-19 earlier. Thus, ventilators were pressed into service to treat sick patients who could not breathe (Póvoa *et al.*,

2020). Now it is realized that the virus causes blood coagulation in the blood vessels of the body parts, especially, lungs resulting in decreased oxygenation of the human body (Price *et al.*, 2020). That is why providing oxygen by ventilators did not help. It was needed to stop the micro clot formation in the lung tissue. Now that is being precisely done by using drugs like Aspirin, Heparin and Clopidogrel (blood thinners that prevent coagulation) as medicinal means of treatment regimens beginning from May- June 2020 (Sivaloganathan *et al.*, 2020).

- (b) Earlier, people used to die on their way to hospitals due to sudden decrease in their oxygen levels in the blood- Oxygen Unsaturation. This was because of Latent Hypoxia- where oxygen saturation was gradually getting reduced, the COVID-19 patients did not have symptoms until it became critically low, to the tune of 65-70%. Normally, one becomes breathless if oxygen concentration gets reduced to below 90% of full saturation. This breathlessness was not noticed in patients. So, ill patients got delayed in reaching hospitals in March 2020. However, after getting wiser on latent hypoxia, oxygen saturation of all patients is monitored using **pulse oxymeter** to make them head to hospital if the saturation plummets to 90% or below. This allows time to medical people to take measures ensuring bright survival chance to the patients since June 2020 (Teo, 2020).
- (c) Earlier, in February-March 2020, doctors did not have drugs to fight corona virus and they treated the complications resulting from it and in the process many people died. Concomitantly, most of the patients became severely infected. But now, doctors know the usage of two important antiviral medicines in COVID-19. The antiviral drug Remdesivir, developed for Ebola virus, has also shown effectiveness in blocking the multiplication (viral RNA replication) of this SARS-COV-2 virus. Favipiravir, another drug against influenza virus, had also acting to stop this viral replication (viral RNA replication). Hydroxychloroquine, the ubiquitous antimalarial drug prevents acidification of endosomes during the process of microbial invasion. It acts on COVID-19 virus too as it also follows the endosome route to establish its crop in human host cells. These all medicines are known as repurpose drugs as they have been used since long to treat other diseases (Jameel, 2020). Through these three drugs, doctors could keep

patients from getting highly infected and, eventually, becoming hypoxic. This knowledge, doctors could only have in August-September 2020, not in February of the same year.

- (d) COVID-19 virus also causes immense harm to bronchi of lungs, especially in males, by causing unassailable inflammatory response of the immune system (Zhu *et al.*, 2020). Recent observations reveal that age old steroid drug dexamethasone, along with other two corticosteroids hydrocortisone and methylprednisolone, could decrease the risk of death in seriously sick people on ventilators or receiving supplemental oxygen, as was the case with former U.S. president Trump. These are the analogues of natural hormones called Glucocorticoids secreted by outer cortical part of the human Adrenal or Stress endocrine gland. The drugs block the expression of cytokines in both white blood cell types- lymphocytes and macrophages. This suppression of immune system going overboard, preventing the so-called cytokine storm, helped a lot. As a matter of fact, this stormy immune response was not only killing the virus but host too. In February-March 2020 doctors did not know how to prevent it from happening but now in September, it is known to them for sure. Such medicines, being used for more than 70 years have come handy in the treatment of this dreaded disease (Singh *et al.*, 2020).
- (e) It has also been found now that hypoxia is relieved by breathing in belly down lying position (Ghelichkhani and Esmaeili, 2020). Further, scientists from Israel have found Alpha Defensin; a chemical produced by the White Blood Cells of patients, inducing the formation of micro clots in lung blood vessels. Satisfyingly, this can be taken care of by a simple **uricosuric medicine**; called **Colchicine**. It has been prescribed in the treatment of Gout, a kind of arthritis occurring due to hyperuricemia, a metabolic disorder of uric acid metabolism (Hoffman, 2020).

So now it is known for sure that patients have a better chance of surviving the COVID-19 infection in February 2021 than that in February-March 2020. Many countries, including India, didn't peak in March or April because of the lockdown clamped over there. This strategy has helped in postponing the COVID-19 pandemic by at least three vital months. It has made governments save many lives. Looking ahead, there's no need to panic from COVID-19 now as the infection has better chances of being stemmed now and of consequent survival than that of a year earlier.

Lets all follow the simple refrains as given below:

1. To wear appropriate masks
2. To keep 6 feet distance from each other
3. To order home delivery of groceries & vegetables
4. To work from home whenever possible
5. To undertake hand washing & maintaining hygiene
6. To stay at home during lockdown
7. Another important thing is to lie down on ones stomach for more oxygen to flow into the lungs. Breathing will be a lot easier, if practiced by both patients as well as healthy persons for 15-20 minutes 4-5 times a day (National Disaster Management Authority, 2020).

Conclusion

Senior citizens, the elderly, must be wary and careful, especially those living with NCDs (Non-Communicable Diseases), viz. diabetes mellitus, coronary heart disease, COPD (Chronic Obstructive Pulmonary Disease) and cancer. Infact, countries suffering severe fatalities have reported far higher deaths among these population groups. Likewise, people suffering from Metabolic Syndrome- a constellation of at least three adverse health conditions amongst- abdominal obesity, hypertension, high blood glucose level, high blood triglyceride level and low blood HDL cholesterol level- are also vulnerable to this disease (Singh and Misra, 2020; Costa *et al.*, 2020). If someone apprehends that everyone is to get infected, give a retort that you want to be the one being ahead of none in embracing the virus. Thus, one must stay humble, not only in relation to COVID-19 but also in life. Humility, as we all know, is the median quality between the two extremes- abject submission and knotty arrogance.

(This article has been written much before the advent of second wave of COVID-19.)

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