



## Various Aspects of Covid – Facts, Knowledge, and Managements

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### Abstract:

The entire world has witnessed the Covid pandemic as the most unexpected, most widespread, and most infectious viral infection leading to severe adverse health conditions, death, and loss of the global economy. Covid came to our doorstep in Dec. 2019 and within four months spread like a dark light all over the world. Each one of the sufferers has something to add to their Covid experience with the common feeling of fear, anxiety, confusion, myths and helplessness. It's been two and half years of the Covid outbreak and it is still present globally but now in a different acceptable, approachable, and acknowledgeable form. The scientific community, the medical fraternity, and health care workers played a major role in overcoming Covid-related challenges, which though the still persist. The awareness about Covid through media, institutions, and governments along with massive scale vaccination programs has brought the situation relatively out of fear and confusion. The awareness and knowledge about the disease have a major role to bring an effective and speedy management. This article will describe various basic aspects of Covid involving its origin, cause, features, current managements, and future direction.

**Introduction:** The Covid pandemic has been witnessed by the world as the most unexpected tragic viral attack leading to severe adverse health conditions, death, and huge loss of the global economy.[1] Covid came into existence in Dec 2019 and within four months, spread all over the world. Despite different situations, each of the Covid sufferers experienced the common feeling of fear, anxiety, confusion, myths and helplessness. It's been two and half years of the Covid outbreak and it is still present globally but now in a different acceptable, approachable, and acknowledgeable form. The scientific community, the medical fraternity, and health care workers has played a major role in overcoming Covid-related challenges, which still persist. The awareness about Covid through media, institutions, and governments along with massive scale vaccination programs has brought the situation relatively out of fear and confusion. The awareness and knowledge about the disease have a major role to bring effective and speedy existing management to the people and look for positive future directions.

**Covid Virus as a new existence.** Ever since the life began on this earth, a large varieties of organisms, species, and animals evolved, many of them got extinct and several of them have still survived in the present world. Viruses among these are supposed the oldest form of life or (boundary of life) and many organisms that evolved in due course of evolution co-lived with viruses including humans.[2] This is why viruses are omnipresent in and out of our bodies. But humans also faced pathogenic viruses which have always been trying to acquire their body's cellular system as a place of their reproduction and increase their population. Human develops a defense system to fight against these viruses in a form of a complex

immune system which is mainly two types, an innate and adaptive system. The former is the non-specific, first line of defense while the latter is specific, and robust but needs a prior exposure to the pathogen as a memory to fight in an effective way. In the context of Covid, (coronavirus infectious disease) also called Covid19 because the disease first spread in year 2019, it is caused by a newly evolved pathogenic virus SARS-Cov-2 (Severe acute respiratory syndrome coronavirus 2) as its structure resembles previously reported SARS Covid virus in the year 2002. It preexisted in bats and suddenly changed its host from bat to human the event is also called as 'Zoonotic spillover,' with high infectivity potential.[3] Since humans never co-lived with it, and their immune systems never encountered it, the adaptive immune system of humans could not handle and fought in a directionless way, leading to adverse body situations that when not controlled on time lead to death. This is the reason, the entire human population suffered due to the emergence of such a virus and this pandemic was established.

**Features of Covid Virus:** The Coronavirus is spherical around 50-200nm size with a series of its proteins on the surface over enveloped capsid. There are three structural surface proteins spike (S) protein, membrane (M), and envelope (E) protein. S-spike proteins provide a crown-like structure to coronavirus and are responsible for binding on the host cell surface receptors.[4] It contains a particular domain-specific to ACE-2 (angiotensin-converting enzyme 2) receptors. These receptors are highly expressed in lungs, heart, kidney, and intestine cells and therefore the primary site of the attack. The affinity of SARS Covid 2 spike protein towards ACE2 receptor is 20 times higher than the previous form of SARS virus.[5] This makes this virus highly infective for respiratory diseases.

Spike proteins itself has two functional subunits S1, which mediate the binding, and S2, that mediate the fusion of viral and cellular membrane. Because of the major role of Spike protein in viral binding, they remain a primary target to develop drugs and vaccines against Covid. The other ‘M protein’ can be seen as profused protein on the viral surface and directs its spherical shape. It can also play its role in interactions with other proteins and viral assembly. The E protein is the smallest protein on the viral surface and plays its role in a viral release after its assembly. The viral envelope is a lipid layer derived from the host plasma membrane. The viral envelope is sensitive to organic solvents and soap and detergents and therefore these reagents are used as disinfectant agents to kill the virus if present on our hands and external body surfaces. Underneath the envelope is the viral capsid the protein covering the viral genome. The capsid consists of N protein which has multiple roles during viral replication and infection. It aids in viral genome replication and also aids in suppressing or evading the host-mediated immune responses. Within the capsid of coronavirus is its genome which is a single-stranded RNA molecule of size around 30k bases largest among all RNA viruses. (Fig.1).

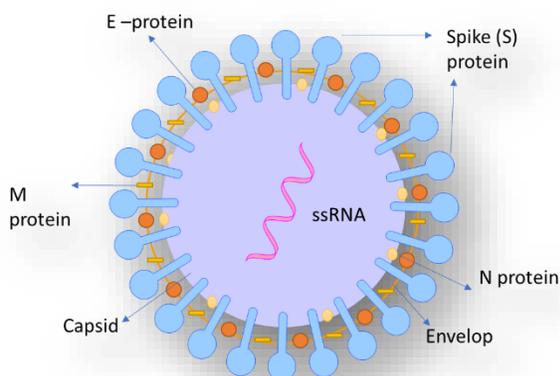


Fig.1: Corona Virus structure

Few earlier studies claimed viral genome capable of integrating in host genome but latest studies does not support the claim and revealed that earlier integration results could be an artifacts or noise.[6]

**Corona Virus infections:** The corona viral infection was initially considered to be highly contagious and had fear or myths to get an infection from all kinds of viral contaminated surfaces. But later studies cleared it that there is a little chance of transmitting the viruses from such surfaces. The primary mode of spread is through droplet infection from an infected person or repeated exposure to an infected environment.[7] When an infected person cough or sneeze those droplets gets aerosolized and get inhaled by a nearby person and the infection spreads. Similarly directly touching the nose or mouth with a contaminated hand allow viral inhalation into our body. The R factor refers to the “effective reproduction number” on average, is 3 for coronavirus signifying every one infected person can infect another three-person. However, the R factor may vary depending upon population density.[8]

**Mechanism of infection:** Once the virus enters the upper respiratory region it targets the mucosal epithelium of the upper respiratory tract where it can bind to ACE 2 receptors to begin its infection cycle. The virus may further reach to lungs’ epithelium and continue its infection cycle. They can enter the cells through two mechanisms. The viral spike protein after binding to the ACE2 receptor trigger it’s the proteolytic cleavage mediated by host cells and allows merging of the virus to the cellular membrane and further inject the viral genetic material into the host cell. The other mechanism of viral entry is receptor-mediated endocytosis. In this scenario, the entire viral particle after getting

attached to the host cell membrane receptor gets buds off inside the cell in a form of the vesicle and paves its way through a variety of membrane trafficking endocytic pathways such as clathrin-dependent, flotillin dependent, caveolae dependent, and micropinocytosis.[9] Each of these pathways is the potential target to develop drugs against viral infection. Once entered inside the cells viral-specific RNA is replicated and translated using host cellular machinery. New viral particles are formed and then released in a form of vesicles to invade surrounding cells. The viral invasion of cells leads to apoptosis and triggers the immune system of the host and their cytokine-mediated inflammatory responses.[10]

**Outcome of infection:** The covid19 infection in the majority of cases causes is mild, moderate symptoms of typical viral infection including fever, cough, and cold but due to a great outreach of this virus a significant range of people also develop severe symptoms including pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure (MOF) and death. The pathophysiology of Covid may involve many complex mechanisms which are still investigative. The virus may cause a direct cytopathic effect. However, the most acceptable mechanism involves virus-induced innate and adaptive responses which recruit cytokine-mediated inflammatory responses. These responses mediate increased vascular permeability which causes fluid leakage into the lungs and more cell-mediated responses. An uncontrollable cytokine response known as ‘cytokine burst’ or ‘cytokine storm’ causes severe inflammation to lungs tissue and blocks the gas exchange leading to respiratory failure. The activation of the complement system, along with cytokine enhances the expression and

secretion of coagulation factors leading and platelet aggregation and causing blood coagulation risking cardiac problems. The excessive damage to the lungs epithelium may cause alveolar fibrosis which may occur both during a post-covid infection. Largely, the disease pathophysiology of covid 19 involves a wide combination of factors primarily regulated by cytokines.[11]

**Post-Covid complications:** Although the patients get recovered from COVID 19 after treatment, the complications related to Covid may still persist and have been shown to be affected multiple systems in many reported cases. These include cardiac arrhythmias, myocardial injury, and sudden deaths due to failure in the cardiovascular system; renal impairment and failure in the urinary system; neurological complications such as encephalopathy, cranial neuropathies, myelitis; increased male infertility and adverse pregnancy outcome in female, gastric irritation and it’s complications in the digestive system: disseminated intravascular coagulopathies, septic shock, hemophagocytosis in the immune and hematologic system; and adverse psychological behavior such as depression, stress, fear, anger, frustration.[12]. A regular medical follow-up is required for such complications.

**Covid Testing:** Molecular testing using real time (RT) PCR which estimates the presence and number of viral genome present in oral and nasal swab samples and measures the viral load is the most widely used for Covid testing. These are sensitive test with high degree of accuracy. Current genes targeted for covid19 testing include RNA-dependent RNA polymerase (RdRP), Envelope gene (E gene) and Nucleocapsid N phosphoproteins (N gene). The average time

for running the samples is 2-3 h and in one run, in an average of 96 samples can be run. The final report with all kinds of analysis and verifications can be prepared in 12 to 24 hr. The RT PCR test though sensitive have chance of providing false results in few cases particularly when the viral strain is mutated. The other kind of test includes serological testing which detects the presence viral antigen or antibody raised against the viral antigen during infection. Though less sensitive these testing can be useful in certain settings such as the finding history of covid infection, seroprevalence in a population and understanding of the Covid-related immunology.[13]

**Covid new mutated strains:** The mutation in SARS Cov2 virus has been continuously establishing due to lack of resistance or immunity against the virus strain. The genetic changes (mutations) in these virus has led to new forms of strains. New emerging strains are listed in table- of starins 1.[14] Among different strain categories, for variants of concern (VOC) scientific evidences are available for their disease spread, for variant of interests (VOI) only preliminary evidence have been established, while for variant under monitoring (VUM) only indications are available and further scientific evidences needs to be collected.

**Table.1: SARS Cov2 Variants**

**VARIANTS OF CONCERN (VOC)**

| SL NO. | VARIANT | Disease Severity | Mutations accumulated (in number) | COUNTRY REPORTED WITH 1 <sup>ST</sup> CASES |
|--------|---------|------------------|-----------------------------------|---|
| 1      | OMICRON | Mild             | 60                                | SOUTH AFRICA                                |
| 2      | DELTA   | Extreme severe   | 17                                | INDIA                                       |
| 3      | ALPHA   | Moderate         | 23                                | UNITED KINGDOM                              |
| 4      | BETA    | Severe           | 13                                | SOUTH AFRICA                                |
| 5      | GAMMA   | Moderate         | 22                                | BRAZIL                                      |

**VARIANTS OF INTEREST (VOI)**

| SL NO. | VARIANT | Mutations accumulated (in number) |
|--------|---------|-----------------------------------|
| 1      | LAMBDA  | 19                                |
| 2      | MU      | 19                                |

**VARIANTS UNDER MONITORING (VUM)**

| SL NO. | VARIANT           | Severity | FIRST IDENTIFIED |
|--------|-------------------|----------|------------------|
| 1      | C.1.2             | Low      | SOUTH AFRICA     |
| 2      | Eta               | Low      | ENGLAND, NIGERIA |
| 3      | Iota              | Low      | NEW YORK         |
| 4      | Kappa             | Low      | INDIA            |
| 5      | B.1.617.3         | Low      | INDIA            |
| 6      | THETA             | Low      | PHILIPPINES      |
| 7      | B.1.1.318 RELATED | Low      | ENGLAND          |
| 8      | C.36.3-RELATED    | Low      | -                |

**Current Management:** The rapid global spread of SARS CoV2 has led to an urgent need for therapeutic inventions emphasizing on vaccines development. The vaccine clinical trials were undertaken through randomized control trials and the results have been found satisfactory. Many companies from different countries could develop the vaccine and are now under usage. (Table 2).[15] The usage of antipyretic and anti-inflammatory conventional drug for symptomatic based treatment are currently in practice. The highly severe cases are kept in ISU with mechanical ventilation

The other form of drug-based management that were initiated at certain stages of covid pandemic as off-label use are no more recommended. This includes anti-Viral drugs such as Chloroquinone & Hydroxy-Chloroquinone which had preliminary usage for the management of SARS CoV2 virus, but the studies reveal high mortality rate substantiating to ventricular arrhythmias with increase in cardiac QT interval and cardiovascular toxicity. Hence, the usage of high dose of chloroquinone as a preliminary treatment in SARS CoV2 virus was withdrawn.

**Table2: Most widely used COVID Vaccines**

| SL NO | VACCINE NAME                          | Brand Name                      | DATE OF OBTAINING EUL          |
|-------|---------------------------------------|---------------------------------|--------------------------------|
| 1     | The Pfizer/BioNTech                   | RNA vaccine                     | 31 <sup>st</sup> December 2020 |
| 2     | AstraZeneca vaccine                   | Vaxzevria / Covishield          | 16 <sup>th</sup> February 2021 |
| 3     | Janssen/Ad26.COV 2.S vaccine          | Johnson & Johnson COVID Vaccine | 12 <sup>th</sup> March 2021    |
| 4     | Moderna COVID-19 vaccine              | Spikevax mRNA vaccine           | 30 <sup>th</sup> -04- 2021     |
| 5     | Sinopharm COVID-19 vaccine            | Sinopharm                       | 7 <sup>th</sup> -05-2021       |
| 6     | Sinovac-CoronaVac vaccine             | Sinovac                         | 1 <sup>st</sup> -06- 2021      |
| 7     | Bharat Biotech BBV152 COVAXIN vaccine | Covaxin                         | 3 <sup>rd</sup> -11- 2021      |
| 8     | CovoVax vaccine                       | CovoVaxN                        | 17 <sup>th</sup> -12-2021      |
| 9     | The Nuvaxoid vaccine                  | Nivaxoid                        | 20 <sup>th</sup> -12- 2021     |

Antibiotics such as Azithromycin was therapeutically used as a 14 days regimen for patients with the initial onset of symptoms of SARS CoV2 virus, and were also used in combination with chloroquine. The reports suggested poor compliance to Azithromycin and was not found to be an effective mode of treatment in the SARS CoV2 virus treatment. [16]

### Potential Covid Drugs

**Lopinavir/Ritonavir:** The combination of Lopinavir and Ritonavir was used national emergency drug in the management of COVID 19. The combination of drugs was effective rather than using it individually and, showed a reduced mortality rate and a better clinical outcome in the treatment of COVID 19 patients. Currently, numerous clinical trials are being undertaken to explore the therapeutic potential of the drug. [17]

**Remdesivir:** Remdesivir has been identified as a promising therapeutic drug in the treatment of COVID 19 outbreaks. It is a prodrug to adenosine analog with antiviral properties by inhibiting viral replication by prematurely terminating RNA transcription. Remdesivir was previously used during the Ebola virus outbreak in Africa. After the outbreak in WUHAN, it underwent in-vitro testing after which it was considered for treatment of SARS CoV2 in patients where the progression of infection to the lung, requiring ventilation was not observed. [18]

**Janus Kinase Inhibitors (JAK) :** JAK is known for autoimmune and anti-inflammatory properties. Cytokine storms are controlled through JAK inhibitors. They also inhibit viral replication and pathogen clearance by controlling the expression of T1IFN. JAK inhibitors may not have target directed approach as treatment option of

COVID 19. Hence, the drug is under trial to see the clinical outcome and long-term administration and complications associated with JAK inhibitors.[19]

**Baricitinib:** Despite the beneficial effects of Remdesivir, the morbidity and mortality still remain the same in COVID 19 patients. Recently, FDA has updated Baricitinib, popularly known by tradename Olumiant, the emergency use authorization in the treatment of COVID 19. It is an oral drug, administered in individuals requiring oxygen supplementation and ventilation. The drug is a selective inhibitor of Janus Kinase 1 & 2 and acts by inhibiting the intercellular cytokine signaling pathway. It increases leukocyte count in patients by impairing AP2-associated protease kinase-1, which is seen elevated in SARS Cov2 cases. The usage of Baricitinib has shown a reduction in selective inflammatory marker levels and improved oxygen levels in COVID 19 individuals.[20]

**Artesunate:** It is a semisynthetic derivative of Artemisinin with Anti- Malarial properties. It is widely used as an intravenous injection in the treatment of Chloroquine resistant Malaria. Artesunate is considered for its potential to induce substantial topological changes in N-terminal nonstructural protein 1 and thus inhibit the SARS CoV2 Nsp1.[21]

**Imatinib:** It is a tyrosinase kinase inhibitor widely used as an anti-neoplastic drug. Patients with COVID 19 exhibit respiratory failure and capillary which is a major cause for increased mortality. The impending ability to reverse capillary leak is the major reason that the drug is considered in the solidarity plus trial.[22]

**Infliximab:** Tumor Necrosis Factor  $\alpha$  (TNF  $\alpha$ ) is a pro inflammatory cytokine with significant role in array of cellular events like

cell proliferation, cell differentiation, cell survival and cell death. Infliximab is an TNF inhibitor thus reducing mortality in patients with COVID-19.[23]

**Future directions:** The world is still struggling with the adverse effect of Covid and many countries are still in the risk of new strain outbreak. However, due to huge scale vaccination programme in many large and populated countries like India, China, USA and European countries, it has generated a wide range of active immunity at the global scale. This immunity does not guarantee prevention against virus attack but significantly subsides the severe effect of the diseases and thus lower the disease burden. Development of new vaccines capable of generating immunity against new strain and new drugs which can be effective and affordable globally are the directions in which health care agencies and organizations are working. In addition, incorporating a preventive and healthy immune boosting life style at global level will further help to fight against this pandemic as ultimately, it personal immune system which is the main protecting weapon against this virus.

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