CLINICAL SYNOPSIS OF COVID-19

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1.1 Introduction:

The world has seen the onset of a pandemic of a new infectious disease from December 2019. This has been formally named as the Corona Virus Infectious Disease (COVID)-19 by a consensus group of WHO experts. Numerous clusters of patients started to surface in Wuhan, Hubei Province, China in mid-December 2019. They presented with features of a viral respiratory illness with complaints off ever, cough, headache and breathlessness. Some of the patients had evidence of respiratory failure, shock, acute respiratory distress syndrome (ARDS) and sepsis. The current global pandemic due to the highly contagious COVID-19 infection is rapidly spreading in many countries with a high number of deaths. Many communities and countries have enforced restrictions, permitting only essential activities. Health systems around the globe are currently preparing to manage the surge of the influx of critically ill patients. During this phase, care providers, administrators, and policymakers work in concert to understand and combat this deadly pandemic. The current knowledge about COVID-19 is limited but rapidly evolving. During this outbreak, the medical community used evidence gleaned from past outbreaks of SARS-CoV and MERS-CoV to predictCOVID-19's behavior, clinical presentation and treatment. In addition, corona viruses are known to cause signs and symptoms of multi-organ system damage, many of which are subtle and can go unnoticed by trained medical professionals.

Furthermore, frontline healthcare personnel lack a comprehensive review of the numerous clinical pulmonary and extra-pulmonary manifestations of deadly corona viruses making self-education time consuming. SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2 is a newly emerging human infectious corona virus, originated in Wuhan, China, and has been spreading rapidly in China and other countries since December 2019.

The World Health Organization (WHO) also declared a global emergency on January 31st due to increasing concerns over its fast spread, and on March 11th the disease was recognized as a pandemic. Since the bases for pathogenesis of this virus and its proliferation is unclear, there is still no vaccine or definitive treatment against it. Thus, medications used against SARS-CoV-2 are mainly based on their effectiveness on earlier strains of corona virus, SARS-CoV and MERS-CoV. Therefore, the immediate introduction of potential COVID-19 treatments can be essential and salvaging. In this article, new potential COVID-19 therapies are briefly reviewed.

1.1.1 Prevention of COVID-19 Entry and Its Transmission:

WHO Director General constitutes a Public Health Emergency of International Concern for the outbreak of COVID-19, recommends the options to prevent the disease in new areas and possible reduction in human-to-human transmission to curtail its further spread that can be achieved by the strict quarantine, which involves the movement restriction or separation from the rest of the population with sustained and intense hygiene measures.

Avoiding mass gatherings in enclosed spaces, maintaining the distance of at least 1 meter from any person with respiratory symptoms (e.g., coughing, sneezing); wearing a medical mask for an adequate level of protection combined with hand hygiene frequently by using an alcohol-based hand rub or soap is recommended.

The people who develop respiratory complications during quarantine period should be specially treated and managed as a suspected case of COVID-19 and further tests should be required to confirm whether positive or negative. The front-line healthcare personnel must use the personal protective equipment (PPE) includes N95 or FFP2 standard masks, gowns, gloves, eye protection shields to protect themselves, patients, and others when providing the care.

1.1.2 Diagnostic Criteria:

The viral research institution in China has conducted preliminary identification of the SARS-CoV-2 through the classical Koch's postulates and observing its morphology through electron microscopy. So far, the golden clinical diagnosis method of COVID-19 is nucleic acid detection in the nasal and throat swab sampling or other respiratory tract samplings by real-time PCR and further confirmed by next-generation sequencing.

1.1.3 Rapid Diagnostic Tests:

In 2nd or 3rd week of illness, various antibodies have been detected in the convalescent serum of the donors. Serological assays to detection of SARS-CoV-2 are in the process of development. They need to undergo clinical trials and the regulatory review process. These assays will help to understand the epidemiology of the disease and detection of asymptomatic infection in a given population. Rapid diagnostic test kits have been recently developed in 4-6 weeks' time. They can detect the SARS-CoV-2 in few hours and can be used as screening tests in certain hot-spot areas of the epidemic. Various commercial and research labs like Bosch and Abbott have launched the rapid diagnostic tests.

These molecular cartridge-based assays have an accuracy of 95% for detection of infection (nasal/throat swabs) and meet various quality control standards as per WHO. They can be used at various points of patient care and no transportation of samples is required. However, the test results by these rapid diagnostic kits need to be confirmed by RT-PCR for SARS-CoV-2.

1.2 The Current Update and Possible Treatment Options for Management of Covid-19:

1.2.1 Renin Angiotensin System (RAS) Inhibitors in SARS-CoV-2 Patients:

RAS and ACE2 inhibitors are widely used in treating patients with hypertension. As described earlier ACE2 is the target receptor for SARSCoV-2 and is highly expressed in epithelial cells in the oral mucosa. Additionally, this protein is widely expressed in immune reactive cells such as macrophages, lungs, blood vessels and intestine. Clinical findings suggest that circulating ACE2 levels were significantly increased in diabetic and cardiovascular patients; however, this protein is aberrantly expressed with ACE inhibitors Lisinopril alone. But the ACE2 activity is not altered correspondingly, while cardiacACE2 mRNA expression was increased with RAS receptor inhibitor Losartan. Combination of Losartan and Lisinopril did not affect theACE2 activity compared with Losartan alone, but on other side, ACE2mRNA was highly expressed with Losartan alone. Thus, there is a lack of correlation between up and down expression of ACE2 mRNA with ACE2 activity. However, there is a debate on the use of RAS and ACE inhibitors in SARS-CoV-2 pneumonia infections and few clinical trials are going on for the usage of Losartan among patients who have not previously administered with RAS inhibitors and are either hospitalized or not hospitalized. The selective ACE2 inhibitor DX600 might show beneficial results inSARS-CoV-2 infections; however, its clinical significance in COVID19has not evaluated. Further, in one promising study, circulating recombinant human soluble ACE2 protein upon intravenous administration produced significant blockade of initial stages of SARS-CoV-2viral entry and infections by preventing the binding of viral spike protein onto cell host cell surface ACE2 receptors.

1.2.2 Anti-Malarial Drugs Inhibit the SARS-CoV-2 Infections:

Chloroquine and Hydroxychloroquine are the class of Quinoline derivatives and widely used to treat malaria caused by *Plasmodiumvivax, P. malaria*, and *P. ovule*. It is the active constituent of the bark of Cinchona (*Cinchona of ficinalis*) plant. Apart from malaria, Chloroquine and Hydroxychloroquine can be used to treat amoebiasis and other autoimmune disorders such as rheumatoid arthritis and lupus erythematosus syndrome. Chloroquine and its derivative Hydroxychloroquine inhibit the hem polymerase in malarial trophozoites, resisting the conversion of heme to hemozoin. Plasmodium species continue to accumulate toxic heme, killing the parasite and exhibits anti-malarial activity. Whereas the antiviral activity of Chloroquine is exerted by diffusing into the host cells and accumulating in endosomes, lysosomes and Galgi complexes, where it is converted into protonated form, then this moiety is deposited in organelles and further involve in raising the surrounding pHs The raised pH in endosomes and lysosomes prevent viral fusion and inhibits the viral entry by endocytosis into the cells.

ACE2 is the target receptor for SARS-CoV and SARS-CoV-2 for viral fusion, however, Chloroquine does not affect the ACE2 levels but down regulated the terminal glycosylation of ACE2. Insufficient glycosylation of ACE2 offers inefficiency to bind with SARS-CoV-2 viral spike proteins and inhibits viral fusion. In the field of nano medicine, Chloroquine/Hydroxychloroquine has been used extensively to understand the mechanism of nano particles uptake into cells. It was used as inhibitor of nano particles uptake via endocytosis pathway. Similar kind of viral particle entry through endocytosis route is proposed to be inhibited by Chloroquine. The combination of Chloroquine or its derivative Hydroxychloroquine with drugs like Remdesivir or Azithromycin demonstrated to produce beneficial effects against this novel virus. However, its use in SARS-CoV-2 therapy has not been approved by US FDA and there are multiple clinical trials going on to evaluate the efficacy of Chloroquine/Hydroxychloroquine. Apart from therapeutic benefits, Chloroquine exerts various side effects such as fever, chills, loss of appetite, blurred vision and insomnia. Additionally, few reports indicated that Chloroquine exerts proarrhythmic effects by increasing the QT interval in the ECG patterns and decreasing the heart rate.

This drug cannot be indicated for the patients who suffer from retinopathy and porphyries. Based on the promising evidences, Chloroquine may become suitable drug for SARS-CoV-2 disease. Further, to improve the efficacy, Hydroxychloroquine may be used in place of Chloroquine.

There were reports suggested the superior antiviral effects of Hydroxychloroquine compared to Chloroquine with better safety profiles. Further, the combinational approach along with other antiviral drugs may be designed to evaluate the efficacy. Other anti-malarial drugs such as Artesunate and Artemisone found to be effective against human cytomegalo viruses, but effect of these compounds on SARS-CoV-2 needs to be evaluated.

Moreover, the severe inflammatory cytokine storm observed in multiple organs may be curtailed by Chloroquine due to its immuneomodulatory effects.

1.2.3 Antibacterial and Anthelmintic Drugs:

Azithromycin is a renowned antibacterial drug belongs to the class of microcline antibiotics. It shows antibacterial activity by binding to bacterial 50s ribosomal subunit and represses the protein synthesis. It is commonly used in the treatment of pneumonia, sinusitis, Lyme disease, skin infections and sexually transmitted diseases. Apart from antibacterial activity, Azithromycin has antiviral activity observed in bronchial epithelial cells infected with rhinovirus, where it increased the production of interferon-stimulated genes. Additionally, its anti-viral activity was reported against Zika virus in human glialcells, where it prevented the virus induced alterations in fetal brain. Also, the combination of Hydroxychloroquine and Azithromycin was found to be effective in SARS-CoV-2 associated pneumonia, where this combination significantly decreased the virus load and involved in the elimination of virus. Energetic based modeling suggests that this drug combination might show the effect on SARS-CoV-2 spike-ACE2complex. Recently Pfizer has reported the necessary data of Azithromycin for SARS-CoV-2 clinical trials. Another anti-biotic and anti-tuberculosis drug Carrimycin being tested to treat theSARS-CoV-2 patients, currently, it is under clinical trials, however, its safety and efficacy need to be established in COVID-19 patients.

The fluoroquinolone antibacterial drug Ciprofloxacin is used to treat respiratory tract infections. Apart from its antibacterial activity, it can reduce the replication of polyoma BK virus. Ciprofloxacin reduced the viral load with IC_{50} value (50% virus inhibitory concentration) of 216.67 ± 16.7 μg/ml, whereas, Coumermyc in showed the IC_{50} value of 10.6 ± 3.9 μg/ml. The amino glycoside antibiotics including Neomycin, Kasugamycin, and Streptomycin inhibited herpes simplex, influenza A and Zika virus replication by up regulating the interferon stimulated genes (ISGs). The polyether antibiotic CP-44161 is recommended to treat varicella-zoster virus infections and also it inhibited the proliferation of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). However, these antibiotics were not tested onSARS-CoV-2.The US-FDA approved anthelmintic drug Niclosamide is also explored as an anticancer, antibacterial and antiviral agent. Also, it was found to be effective as a protease inhibitor in shedding the SARS-CoV and MERS-CoV replication and viral antigen synthesis was suppressed by Niclosamide at 1.56 μ M. It might be a good pharmacological agent to treat SARS-CoV-2 infections as well and studies may be designed to evaluate the same in vitro and clinical conditions.

The FDA approved ant parasitic drug Ivermectin is widely used as an essential medicine to treat lymphatic filariasis, strongyloidiasis, ascariasis, head lice, scabies, and river blindness etc. Ivermectin was tested for its repurposing anti-viral activity against SARS-CoV-2, where it has own excellent antiviral activity. The in vitro results suggest that Ivermect in reduced viral RNA load>5000 fold with 5 μ M concentration at 48 h. It might be a good repurposing drug in treatingSARS-CoV-2 infections and further studies are required for this specific use.

1.2.4 Antiviral Drugs:

An American biotechnology company Gilead Sciences developed the antiviral drug Remdesivir (GS-5734) against Ebola virus. Remdesivir exerts broad-spectrum antiviral activity and showed beneficial results in SARS-CoV and MERS-CoV induced respiratory infections. It has been recommended to administer to SARS-CoV-2 infected patients in United States of America, Europe, and Japan, where physicians found the beneficial results. But it is not yet approved by the drug regulators for treating the patients who are suffering from SARS-CoV-2.Remdesivir is a pro drug and is metabolized to its active form GS-441524, which is a nucleotide analogue inhibitor of RNA-dependent RNA polymerases. It interferes with the viral RNA polymerase activity and further inhibits the viral exoribonuclease involved in proofreading and ultimately causes the deprivation of viral RNA production. Remdesivir was tested in clinical isolates of SARS-CoV-2*in vitro*, where it exhibited significant antiviral activity. Further, it was also tested in combination with Chloroquine and found to be effective against COVID-19.

However, the data available is limited on Remdesivir and further studies need to be conducted to prove its essential role in treating COVID-19 along with its drug-drug interactions and contraindications. Oseltamivir is recommended to treat and prevention of Influenza A and Influenza B viruses. It belongs to the class of neuraminidase inhibitors and acts as a competitive inhibitor of neuraminidase enzyme present in influenza virus and prevents the respiratory tract infections. This enzyme involved in the cleavage of the silica acid which is an important component of glycoprotein's presents on the surface of human cells and helps new visions to exit the cells.

The therapeutic potential of Oseltamivir on SARS-CoV-2 infections needs to be evaluated. Few of the combinational drugs such as ASC09F and Ritonavirare being evaluated together with Oseltamivir, these are under the clinical trials now. Corona viruses are associated with different types of proteases such as main protease (Mpro) also known as three chymotryps in-like protease(3CLpro), papa in-like proteases (PL pro) and transmembrane protease, serine 2 (TMPRSS2). Mpro involved in viral replication and plays a pivotal role in processing the polyproteins, which are translated from its RNA. Among all, pyridine-containing α-ketoamide compound 13b inhibited the SARS-CoV-2 Mpro with IC50 value of0.67 ± 0.18 μ M and showed improved safety and lung tropism as well as suitable for inhalational route of administration. In another hand, the virtual screening for approved drugs using 3D model of SARS-CoV-2 Mpro with the help of the crystal structure of SARS-CoV, which is having almost 96% similarity. They proposed and considered nearly 16 candidates and among Ledipasvirand Velpatasvir are attractive and might be effective in treating COVID-19 with minimal side effects. Apart from these, Remdesivir, Saquinavir and Darunavir, as well as flavones and coumarone derivatives were found to be effective againstSARS-CoV-2 Mpro.

Another SARS-CoV-2 protease PL pro plays an important role in viral replication and survival, which mainly involved in cleaving the viral polyproteins, compounds isolated from Alpinia officinarum and ginger having SARSCoV-2 PL pro inhibitory activity confirmed by molecular docking studies. Also, virtual docking studies support that Chloroquine and form sterol also found to be effective against SARS-CoV-2 PL pro. In contrast to others, Bagherzadeh et al. proposed that dual protease Mproand PL pro inhibitors Valaganciclovir, Nelfinavir, Merimepodib, Remdesivir, Inarigivir, Taribavirine and TAS106-106 are suitable inCOVID-19 therapy, among all Remdesivir and Inarigivir showed highest binding affinity. Cam stat maculate is TMPRSS2 inhibitor, is involved in proteolysis processing of spike proteins and it suppressed theSARS-2-S-driven fusion into Caco-2 and Vero-TMPRSS2 cells and might be effective in COVID-19 therapy. Other protease inhibitors include Lopinavir and Ritonavir were found to be effective in SARS-CoV infections and also these drugs are currently under the clinical trials for testing the efficacy and safety against SARS-CoV-2. Investigators performed an open-label randomized trial at Wuhan hospital, China.

They have given the treatment to adult SARS-CoV-2 patients with oral Lopinavir and Ritonavir (400and100 mg, respectively) twice daily for 14 days. They found that Lopinavirand Ritonavir combination was significantly effective againstSARS-CoV-2. However, further studies are needed to draw a clearconclusion on the usage of the combination of Lopinavir and Ritonavirin SARS-CoV-2.

The nucleoside analogue Ribavirin has extensive activity against DNA and RNA viruses and it is used to treat SARS-CoV patients. The exact antiviral mechanism of Ribavirin has been studied for decades and it is still unclear. Ribavirin usage is associated the major side effect of anemia which is found in 27-59% of patients. The importance of Ribavirin for fighting against SARS-CoV-2 was evaluated in combination with protease inhibitors and corticosteroids. This drug has been showing significant results with so fosbuvir and this combination is under the clinical trials (NCT01497366).The nucleotide analogue Sofosbuvir is used to treat hepatitis C and it is recommended in combination with Ribavirin, Velpatasvir, and Voxilaprevir.

Molecular docking studies of RNA dependent RNA polymerase model suggest that Sofosbuvir in combination with Ribavirin and Remdesivir could exhibit possible therapeutic effects in SARSCoV-2. Basically, Sofosbuvir is a pro drug, which converts into active metabolite GS-461203 (2′-deoxy-2′-α-fluoro-β-C-methyluridine-5′-triphosphate) and serve as a defective substrate for the non-structural protein 5B (NS5B) of RNA dependent RNA polymerase and further inhibits RNA synthesis.

Sofosbuvir and other combinations will be tested in the view of adverse effects such as purities, upper respiratory tract infections, and lymphopenia. The short-term anticoagulant, antiviral and antibacterial drug Nafamost maculate inhibits Spike protein induced membrane fusion in MERS-CoV and also researchers suggested that using Nafamost at alone or with combination of antiviral drugs could be a safe approach in treating COVID-19.

1.2.5 Effect of Interferon's on SARS-Cov-2:

The 166 amino acid sequence of Interferon alfacon-1 is produced by recombinant DNA technology, which is the class of non-naturally occurring type-I interferon. Interferon alfacon-1 acts as anticancer and antiviral agent. The therapeutic effect of Interferon alfacon-1 was observed in leukemia, melanoma, HIV/AIDS related Kaposi's sarcoma, and hepatitis C. It is also found to be effective in SARS-CoV and also tested in SARS-CoV-2 in combination with corticosteroids. Interferon alfacon-1 shows antiviral activity by binding to interferon receptors type 1 including IFNAR1 and IFNAR2c. Further, it initiates the demonization and activates the Janus kinas 1 (Jak1) and tyrosine kinas 2 (Tyk2) phosphorylation.

The signal transducers and activators of transcription 1 and 2 (STAT1 and STAT2) bind to the phosphorylated IFNAR and initiate the expression of immuneomodulatory and antiviral protein expression including protein kinas R (PKR) and 2′-5′ oligoadenylate syntheses (2′-5′ OAS). Additional clinical studies are required to approve this drug for SARSCoV-2 therapy.

There are multiple reports on the antiviral activity of IFN-α and IFN-β, and combinations of IFN-α/β, IFN-β 1a and IFN-γ against SARS-CoV and these agents might be also effective againstSARS-CoV-2 too, which need to be evaluated in suitable studies.

1.3 Therapeutic Importance's of Amniotic Fluid Cells and Convalescent Plasma in SARS-CoV-2 ARDS Infections:

Amniotic fluid cells are the possible source of stem cells for clinical purposes such as fetal therapies and regenerative medicine, where they proliferate rapidly can differentiate into different cells. The human amniotic fluid is approved by US-FDA for tissue injury and also used to treat inflammatory and fibrotic diseases. The researchers from the University of Utah tested the nebulizer and/or intravenous purified amniotic fluid in SARS-CoV-2 patients, where it reduced the respiratory inflammatory responses observed with this novel pandemic virus. Recently they received the approvals from regulatory bodies to perform the clinical trials (NCT04319731).

1.3.1 Monoclonal Antibodies to Treat SARS-CoV-2 Infection:

Monoclonal antibodies are currently used for diagnostic and therapeutic purposes. Various monoclonal antibodies are approved by USFDA to treat cancer and autoimmune disorders. Additionally, few of monoclonal antibodies are tried to treat SARS-CoV-2 infections such as Bevacizumab (NCT04305106), Tocilizumab (NCT04317092), and Meplazumab (NCT04275245) etc. The SARS-CoV- specific human monoclonal antibody, CR 3022, which has the ability to bind with SARS-CoV-2 RBD (KD of 6.3 n M). CR3022epitope was not overlapped with the ACE2 binding site within SARSCoV-2 RBD. This novel monoclonal antibody might be effective clinically for treating SARS-CoV-2 associated pneumonia. Human-to-human transmission of SARS-CoV-2 is possible due to interaction of spike protein with human ACE2; thus, spike protein is the main target for antibody-mediated neutralization. Various neutralizing monoclonal antibodies are tested against SARS-CoV including 80R, CR 3014, CR3022, m396, B1, 201, 68, 1F8, and 5E9, these antibodies might play an important therapeutic role in SARS-CoV-2 infections. Collectively, spike proteins, ACE2 and their interactions are the main targets for developing new therapeutic monoclonal antibodies for treating SARS-CoV-2 infections.

Tocilizumab is used in autoimmune diseases such as rheumatoid arthritis and multiple myeloma and it is a human recombinant IL-6receptor (IL-6R) antibody. It is associated with major side effects such as allergy, liver toxicity and hyperlipidaemia. IL-6 is involved in the activation of various immunological and inflammatory mediators, which are responsible for respiratory collapse observed inSARS-CoV-2 infected patients. Tocilizumab is under phase II clinical trials and tested for SARS-CoV-2 induced pneumonia (NCT04317092).Another IL-6R monoclonal antibody Sarilumab is under clinical trials for SARS-CoV-2 (NCT04315298). It is widely used in the treatment of rheumatoid arthritis and it suppresses the IL6R mediated inflammation.

Cytokine storm is responsible for the pneumonia condition in SARS-CoV-2 infected patients. Clinical trials on Sarilumab and Remdesivir have been initiated to test the therapeutic efficacy against SARS-CoV-2. The potential therapeutic role of Sarilumab in COVID-19 need to be further confirmed in clinical conditions.

1.3.2 Natural Products and Dietary Supplements:

Our diet contains a lot of vitamins, minerals, carbohydrates, proteins, fats, and lipids and they play an important role in maintaining the homeostasis in our body and play important role in maintaining the immunity. Additionally, our diet contains various biological active natural products and they exert multiple pharmacological properties such as anticancer, antioxidant, anti-inflammatory, anti-diabetic, antibacterial, antiviral and antifungal properties etc. The battery of pro inflammatory cytokines is responsible for the cytokine storm, which is involved in manifestation of severe acute lung injury this is the main cause for SARS-CoV-2 induced morbidity and mortality. The active constituent of turmeric, Cur cumin exhibits wider pharmacological activities such as anti-bacterial, antiviral, anticancer, anti-diabetic properties. Cur cumin inhibited pro-inflammatory cytokines IL-1β, IL-6, and TNF-α level and suppressed the cytokine storm in Ebola virus infected experimental models.

Additionally, Cur cumin also inhibited the SARS-CoV replication and the effective concentration (EC_{50} value) was found to be around 10μ M and also acted as a protease inhibitor. Thus, it might be effective against SARS-CoV-2 infections, where intravenous (I.V.) route of administration in suitable formulation form may enhance the better bioavailability. Similarly, a thorough search across all the natural products needs to be evaluated for their direct antiviral effects and their potential role in controlling severe inflammatory responses observed in COVID-19 induced pneumonia.

The Indian traditional plant Neem (Azadirachta indica) and its parts such as leaves, seeds, flowers, barks and routes are widely using in various diseases. Ancient people believe that it is a Sarva roga nivarini (the cure for all diseases). Methanolic extract of neem leaves exhibited antiviral activity against HSV-1 infections by glycoprotein mediated viral fusion. Nimbolide is an active constituent of Neem tree explored as a pharmacological modulator in treating various diseases such as cancer, diabetes, and inflammatory diseases. TNF-α is apheliotropic cytokine involved in activation of various signaling cascade and this cytokine might be playing role in respiratory failure associated with COVID-19 mediated pneumonia. Nimbolide is found to be TNF-α inhibitor and also suppresses the nuclear translocation of p65 NF-κ Band HDAC-3 and inhibited the cytokine storm observed in ARDS experimental model. Thus, it might show beneficial effects in SARSCoV-2 infections by direct antiviral activity or indirect supportive therapy by controlling the inflammatory cytokine storm. This natural product may have clinical significance in inflammation associated with viral diseases.

The other natural product with a ferine A is isolated from Ashwagandha (With ania somnifera) and widely used to treat various diseases such as cancer, fibrosis, and inflammatory disorders. It has shown the antiviral activity against Herpes Simplex virus 1 and 2, which may show plausible effects against COVID-19.Andrographolide is a diterpenoid isolated from Andrographis paniculata, which has been employed in treating various diseases such as cancer and inflammatory diseases. Apart from anti-inflammatory activity, andrographolide exhibits immuneomodulatory effect by increasing the level of cytotoxic T-cells, NK cells, phagocyte cells.

1.3.3 Vaccines for Corona Viruses:

The epidemics of SARS (2003), MERS (2012) and the recent SARS-2 (2019) has generated a lot of interest in the preventive strategies like the drug chemoprophylaxis for health care individuals and close contacts of index patients of the COVID-19. The role of drugs has been discussed in a separate section. After the SARS epidemic in 2003, various researchers all over world got in the effort of developing a candidate vaccine for the same. There are about 43 vaccines that have been developed. However, most of them are in the pre-clinical phase. They are yet to undergo phase 1 randomized trials in humans.

These vaccines are DNA, inactivated, live attenuated vaccines (LAV), viral vector based (non-replicating) protein sub-unit vaccines and other 6 unknown vaccine types.37 One of the RNA based vaccines (LNP-encapsulated mRNA) has been made available for the phase 1 clinical trial in humans. This vaccine has been developed by collaborative effort of scientists at NIAID/NIH and a biotechnology company (Moderna Therapeutics) in USA.

The clinical trial began in mid-March 2020 and has already enrolled few patients in Seattle, USA (NCT04283461). It will study the efficacy and adverse reactions of the candidate vaccine in 45 adult volunteers from 18 to 55 years of age. Another vaccine that has gone in phase 1 clinical trial is a non-replicating viral vector vaccine (ChiCTR2000030906). It has been bioengineered by using an adenovirus vector (type 5) at Beijing Institute of Biotechnology and Can Sino Biological Inc. It uses the same platform as was used for developing a vaccine for Ebola virus. However, this is just the beginning and it will take 12-18 months for the trial to complete and have the data to interpret for antibody response and long-term efficacy.

1.3.4 Host Immune Responses:

An understanding of the various host cell immune responses evoked by the corona viruses may help us to develop effective drugs and vaccines for this infection. Various researchers have studied the T-cell immune response to SARS-CoV in the past. Recently with the evolution of the SARS-CoV-2 or COVID-19 epidemic in China a resurgence of interest in the immune mechanisms has been generated. An innate immune response evoked by the macrophage activation leads to a T-cell mediated response. The macrophages present CoV antigens to the T-cell subsets (Th 17) which lead to a massive release of various cytokines like IL-1, IL-6, IL-8, IL-21, TNF-b and MCP-1. This is responsible for the immune amplification. These cytokines and chemokines are responsible for recruitment of lymphocytes and other leukocytes to the site of inflammation. This immune amplification is partly responsible for the tissue damage in the respiratory alveoli, bronchioles, pulmonary interstitial walls etc. The increased expression of the inflammatory mediators has a down regulatory effect on NK cells and CD8 cells, which are important for the lymphocytes to clear the virus. Binding of the S-protein to various host cell receptors like ACE2 and DPP4R enables the viral RNA to gain entry in the host cell cytoplasm. Various toll like receptors (TLR) like TLR-3, TLR-4 are important to either evade the immune response or recognition of S-protein. The S-protein recognition leads to activation of pro-inflammatory cytokines.

1.3.5 Conclusion:

-The current COVID-19 pandemic is the third major global illness due to a novel corona virus. Understanding COVID-19 along with the other known novel corona viruses places the newest corona virus in context. We presented the similarities and differences in pathogenesis, manifestations, and outcomes with respect to a spectrum of extra-pulmonary organ systems. Increasing knowledge about COVID-19literature will aid in earlier recognition and more effective therapy. Corona virus infections have led to few epidemics and a new pandemic in last 2 decades. The infections vary in clinical manifestations from self-limiting viral respiratory tract infections or gastroenteritis to severe form like the SARS-CoV-1, MERS and the recent SARS-CoV-2 infections. These have led to a significant morbidity and mortality and a global economic crisis. Newer developments in therapeutics, preventive therapy in the form of chemoprophylaxis and vaccines are underway. Newer information about the molecular mechanisms, clinical manifestations, epidemiological pattern and preventive public measures is available each week in all the scientific or medical journals. In addition, lot of input is being provided by electronic and print media for public awareness.

Only few articles published in the initial phase of COVID-19epidemic have been cited to maintain brevity of the article. It will not be appropriate if a little note is not made about the unsung heroes of this pandemic. The world's 'new heroes' are the medical workers. The doctors, nurses, paramedical staff and other healthcare workers who are directly or indirectly involved with patient care in isolation wards and critical care areas. They risk their own lives, knowing that there are no effective drugs or vaccines available at present.

1.3.6 Future Perspective:

Over the past 50 years, in the pre-SARS era, many different CoV shave been identified that caused a wide variety of human and veterinary diseases. In particular, the human CoV were found to cause mild respiratory diseases. In November 2002, SARS-CoV infection was emerged in Guangdong Province of China, identified to be fatal resulting in ARDS, which became a pandemic in 37 countries with over8000 reported cases and 800 deaths. This deadly SARS virus was found to be originated from horseshoe bats that transmitted to pangolins before reaching humans. At that time no specific drugs or vaccines were available and only preventive measures were implemented to limit the transmission rate by maintaining social distance, quarantine, travel restrictions, patient isolation. In 2012, another zoon tic CoV were identified from Saudi Arabia postulated to have originated from the dromedary camels which infected 2494 people and 858 deaths were reported, in late December 2019, a recent global outbreak, a novel CoV strain has been evolved which is linked to a seafood market in Wuhan, Hubei Province, China with the symptoms varying from mild respiratory illness and pneumonia in most of the patients, to fatal consequences that progresses to ARDS by the induction of a pro-inflammatory cytokine storm. As of 8 April 2020, approximately 1.43million cases of COVID-19 have been confirmed worldwide, and this pandemic is rapidly escalating all around the globe and most of the countries implemented the most restrictive mass quarantines that led to severe global socioeconomic disruption which has become the greatest concern of WHO. As of now, there are no specific approved drugs for treating SARS-CoV-2 and currently, physicians are using the repurposing drugs such as Chloroquine/Hydroxychloroquine, Remdesivir, Tocilizumab, Azithromycin, Dexamethasone, and Acetaminophenetc. They are showing plausible results, however more studies are required for specific use against SARS-CoV-2. Moreover, immune boosters such as Vitamin C, Zinc and other natural products are suggested in preventing the viral infections. Additionally, scientists are developing the new antiviral drugs and vaccines, and few are under the clinical trials. Apart from traditional drug therapy, medical practitioners are transfusing the convalescent plasma to rescue the critically ill patients with successful outcome in viral load reduction; Also, MSCs were effective for treatment with encouraging improvement with fewer side effects. Thus, there is a lot of scope to develop antiviral drugs and vaccines against SARS-CoV-2; there is a need for vigorous effort on the vaccine development and exploration of potential antiviral treatment regimens. Simultaneously, the primary and intermediate host and mechanism of its cross-species spread and human interface needs to be investigated.

Owing to the fact that new CoV viruses will continue to evolve on the basis of their ability to undergo frequent recombination's of their genomes, mutations, the propensity to infect multiple species and the increasing human-animal interface, the strict legislations should be made to prohibit the consumption and farming of terrestrial wild animals to prevent the future outbreaks.

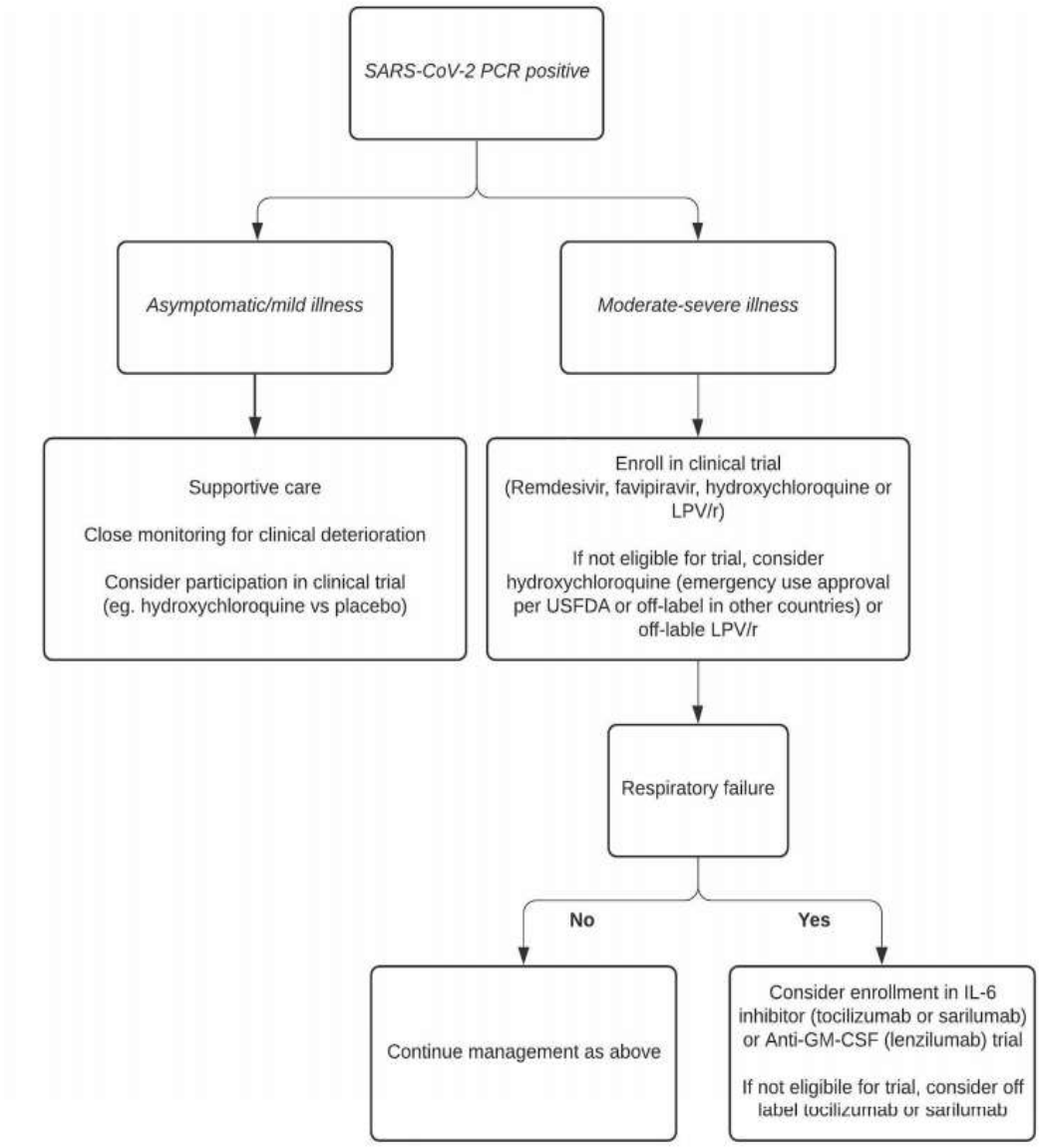

Figure 1.1: Hypothetical Algorithm for Treatment of Corona virus Disease 2019

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2. Immunity Booster on COVID-19

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2.1 Introduction:

Corona virus disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2). It was first identified in December 2019 in Wuhan, China, and has since spread globally, resulting in an ongoing pandemic [2, 3]. As of 10 June 2020, more than 7.3 million cases have been reported across 188 countries and territories, resulting in more than 413,000 deaths with more than 10% mortality rate.

The corona virus (COVID-19) is having very high transmission rate among humans and it and it had transmitted throughout the globe, it is critical to practice the preventive measures to protect ourselves against these viruses. According to WHO's recent report viral diseases are world's highest public wellbeing challenges. (WHO, 2020).

The World Health Organization (WHO) estimates occasional flu brings about 3-5 million cases every year. Today understand hygiene and social distancing are the key practices in protecting yourself as well as other people from getting an infection while additionally easing back the spread of the Virus.

COVID-19 or 2019 novel Corona virus was declared as a pandemic by the World Health Organization in Feb 2020 and keeping in mind that the various countries are thinking about approaching threats that this virus poses to mankind, there are limited measures that people can take to battle this pandemic.

Covid-19 attacks people with low immune systems and people especially people of under and over ages. The immune system is built on beneficial live bacteria that live in the gut which protect the human body from various diseases. When the immune system response is low, weak, or damaged, it becomes an open invitation for infections such as corona virus or other diseases like diabetes, heart disease, or cancer.

Plant-based foods increase and help the intestinal beneficial bacteria, and the overall gut micro biome health which makes up to 85% of the body's immune system. On the other hand, excess of animal foods deplete the body from good bacteria, promote inflammation, and are the underlying cause of diabetes, chronic obstructive pulmonary disease cardiovascular diseases, hepatitis B, cancer, and chronic kidney diseases.

With the 2019 corona virus COVID-19 pandemic, it's especially important to understand that no supplement, diet, or other lifestyle modification other than physical distancing, also known as social distancing, and proper hygiene practices can protect any and proper hygiene practices can protect any person from COVID-19. Currently, no research supports the use of any food supplement to protect against COVID-19 specifically. Our immune system consists of a complex collection of cells, processes, and chemicals that constantly defends body against invading pathogens, including viruses, toxins, and bacteria. 'Keeping our immune system healthy year-round is key to preventing infection and disease'. Making healthy lifestyle choices by consuming nutritious foods and getting enough sleep and exercise are the most important ways to boost our immune system. In addition, research has shown that supplementing with certain vitamins, minerals, herbs, and other substances can improve immune response and potentially protect against illness.

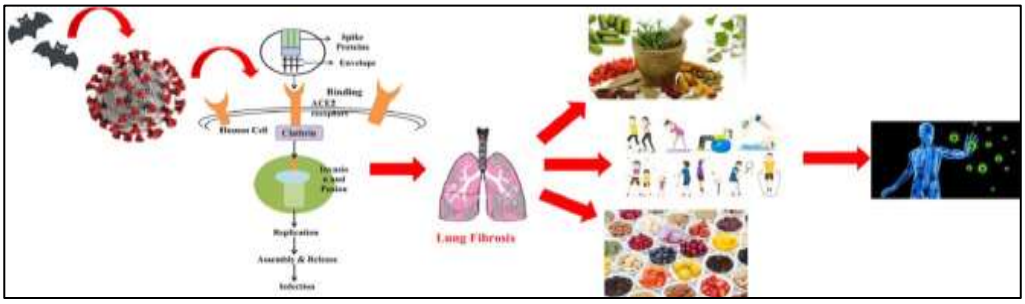

Figure 2.1: A General Overview on Corona virus:

SARS-CoV-2, provisionally known as 2019-novel corona virus, is an enveloped positive-sense single-stranded RNA virus that belongs to the subfamily Orthocoronavirinae, and the family Corona viridae. Subfamily, Orthocoronavirinae, includes four genera, namely alpha, beta-, delta- and gamma corona virus. Predominantly, alpha-and beta- CoV s infect mammals, whereas the main targets of delta- and gamma-CoV s are avian species. With the outbreak of recent SARS-CoV-2 total of seven human-susceptible CoV s strains have been currently identified that can infect human population.

Most of these viruses tend to cause mild infections; however, SARS-CoV identified in 2002, MERS-CoV identified in 2012 and ongoing pandemic caused by SARS-CoV-2 have emerged as fatal CoV s capable of causing severe respiratory tract infections. Genomic sequencing analyses have revealed the close evolutionary relationship of SARS-CoV-2 with other beta-CoV s.

It resembles more with Sarbecovirus subgenus that comprises of SARS-CoV than that of MERS-CoV s of Merbecovirus subgenus origin. At the nucleotide level, SARS-CoV-2 shares 79% homology with SARS-CoV, whereas only 50% with MERS-CoV s. Moreover, SARS-CoV-2 just like SARS-CoV utilizes the same ACE2 receptors to infect its hosts.

Thus, the sites where ACE2 protein is mainly expressed are the potential target sites for SARS-CoV-2 respectively. These regions are belonging to type II alveolar cells of the lungs and enterocytes of the small intestine.

Nevertheless, there are some remarkable biological differences between the SARS-CoV-2 and the other beta-CoV s, which probably make it more infectious. Consequently, the epidemiological dynamics of SARS-CoV-2 is different from previous human-CoV outbreaks having striking local and global spread. Although, SARS-CoV-2 shows greater human-to-human transmission efficiency, its crude fatality rate (0.25% to 5%) is comparatively far less than that of SARS-CoV which is approx. 10%. Furthermore, SARS-CoV-2 has R0 (basic reproduction number) of 4.7 to 6.6.

This highly contagious nature of SARS-CoV-2 is supported by the fact that its spike (S) protein possesses 10 to 20 time's greater affinity for ACE2 receptors than SARS-CoV. S-protein is the surface glycoprotein that assists the virus in the attachment to the host cells through its receptor-binding domain (RBD). S-protein has several domains, one of the sections termed as ectodomain has two subunits, S1 and S2, which form a crown-like structure around the virus. Besides, S-protein of SARS-CoV-2 contains a furin-like cleavage site at the S1–S2 junction, missing in other members of its sister clade. This additional cleavage site might also be responsible for greater pathogen city of SARS-CoV-2 as it also occurs in highly infectious form of influenza virus but lacking in less pathogenic ones.

2.1.1 Supplementing Immunity:

A good strategy is to selectively increase nutrients that may be lacking in our climate and in diet. Vitamin D, for instance, is likely to be low in individuals who live in northern climates with less sunlight. For normal levels, a daily supplement of about 600 to 800 IU of vitamin D is suggested, but with lower levels, a medical consultation is advisable. Since this is a fat-soluble vitamin, it should be taken with fatty foods to maximize the absorption. A healthy sprinkle of herbs like garlic, ginger, rosemary, oregano, and turmeric will also introduce natural anti-inflammatory compounds, which also help to fend off respiratory viruses.

2.1.2 Improve Diet:

The food eaten plays a key aspect in determining overall health and immunity. Eat low carbohydrate diets, as this will help control high blood sugar and blood pressure. A low carbohydrate diet will help slow down diabetes and focus on a protein-rich diet to keep in good shape to any human. And regularly consume vegetables and fruits rich in Beta carotene, Ascorbic acid and other essential vitamins. Certain foods like mushrooms, tomato, bell pepper and green vegetables like broccoli, spinach are also good options to build resilience in the body against pathogenic infections. In diet daily includes supplements rich in omega 3 and 6 fatty acids, if stepping out to buy groceries is not an option during social distancing. Some natural immunity supplements include ginger, gooseberries (amla) and turmeric. Some of these super foods are common ingredients in Indian dishes and snacks. There are several herbs that help in boosting immunity like garlic, Basil leaves and Black cumin. Certain seeds and nuts like sunflower seeds, Flax seed, pumpkin seeds and melon seeds are excellent sources of protein and vitamin E.Probiotics like Yoghurt, Yakult and fermented food are also excellent sources to rejuvenate the composition of gut bacteria, which is important for nutrient absorption by the body.

These are good options for the older generation too in these pandemic days here are some key nutrients that play a role in immunity boosting.

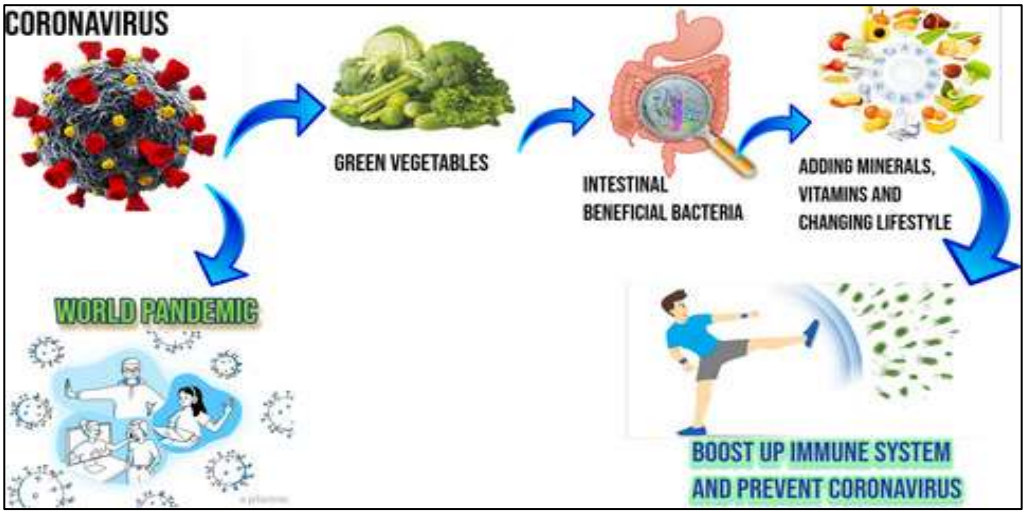

Figure 2.2: Relation between Good Food and Healthy Gut:

A better place to begin is diet, as per health specialists, 80% of the body's immune system is in the gut. A strong gut will give a more significant level of resistance. The Mediterranean diet is a healthy alternative with its focus on fresh fruits and vegetable, whole grains, fatty fish, nuts, and olive oil. The diet gives a lot of nutrients, including vitamin A, B2, B6 and B12, C, D, and E.

Additionally gives zinc, iron, selenium, and other plant-derived minerals and cancer prevention agents i.e. food rich in antioxidants. As per the instruction of WHO consume diet rich in fruits and vegetable locally available in market which boost the immune system i.e. Citrus fruits like orange, grape as well as banana and apples, root vegetables such as carrot, turnips and beetroot.

At long last, it gives healthy fats from fish oil. Recent research propose older adults on a Mediterranean-style diet who additionally took a vitamin D supplement of 400 IU/day had demonstrated increased level of healthy

T cells in one year, demonstrating a positive impact on immunity. Whole foods is always more advisable, and a healthy dosage of matured food sources i.e. fermented foods, including sauerkraut, yogurt, and kefir (fermented milk product), depending upon the nearby culture, is likewise encouraged. Fiber and lentils are likewise food to eat for healthy gut micro-biomes.

In addition, there are evidence that nutrition and other way of life estimates impact immune capacity and susceptibility to infectious illnesses [5].Whether these measures do or don't impact susceptibility to COVID-19 or its clinical course isn't yet known.

2.2 Immunity-Boosting Vitamins and Minerals:

Figure 2.3: Covid-19 Immune System Boosters

For supporting immune system, one can eat immunity supporting foods rich in vitamins like citrus fruits, broccoli, and spinach. It can be helpful to supplement with key vitamins and minerals that may have become depleted like Vitamin C, Vitamin E, Vitamin B, Vitamin D, and Zinc, Magnesium etc.

2.2.1 Vitamin D:

Vitamin D is a fat-soluble nutrient essential to the health and functioning of immune system. Vitamin D regulates the production of a protein that selectively kills infectious agents, including bacteria and viruses. Vitamin D enhances the pathogen-fighting effects of monocytes and macrophages — white blood cells (WBC) that are important parts of immune defense — and decreases inflammation, which helps promote immune response. Specifically, Vitamin D alters the activity and number of WBC, known as T 2 killer lymphocytes, which can reduce the spread of bacteria and viruses. Many people are deficient in this important vitamin, which may negatively affect immune function. In fact, low vitamin D levels are associated with an increased risk of upper respiratory tract infections, including influenza and allergic asthma. Some studies show that supplementing with vitamin D may improve immune response. In fact, recent research suggests that taking this vitamin may protect against respiratory tract infections. In a 2019 review of randomized control studies in 11,321 people, supplementing with vitamin D significantly decreased the risk of respiratory infections in people deficient in this vitamin and lowered infection risk in those with adequate vitamin D levels.

This suggests an overall protective effect. Other studies note that vitamin D supplements may improve response to antiviral treatments in people with certain infections, including hepatitis C and HIV Depending on blood levels, anywhere between 1,000 and 4,000 IU of supplemental vitamin D per day is sufficient for most people, though those with more serious deficiencies often require much higher dose. Sources: our exposure to sunlight, given the right season (not or limited during water depending on latitude) and enough time in the sun, has an important role in determining our vitamin D status. With the help of sunlight, Vitamin D is synthesized in the skin from a precursor derived from cholesterol. Vitamin D exists as either Vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol). Oily fish-such as salmon, herring, mackerel, red meat, Liver, egg yolk, fortified foods such as-most fat spread and some breakfast cereals.

2.2.2 Vitamin C:

Vitamin C is an important aspect of improving immunity, for the kids, adults, or even elderly people. Fruits like oranges, papaya, kiwi, and guava are rich in vitamin C and should be included in diet. Moreover, some vegetables like eggplant, bell peppers, beetroots, spinach, and cauliflower are known to be quite rich in vitamin C and are good for immunity. Green vegetables like broccoli, mushrooms, and even kale are a few immunity boosters that one can include in the diet. They improve the immune system of older people quite rapidly. Berries can also be included in the diet along with foods rich in omega-3 fatty acids—beans, flax seeds, and even some nuts. Elderly people should consume Spirulina and Curcumin, as they are extremely rich in vitamin C and minerals. These super foods help in building and strengthening immunity at great level. Vitamin C increases blood levels of antibodies and helps to differentiate lymphocyte (white blood cells), which helps the body, determine what kind of protection is needed. Some research has suggested that higher levels of vitamin C (at least 200 mg) may slightly reduce the duration of cold symptoms.

One can easily consume 200 mg of vitamin C from a combination of foods such as oranges, grapefruit, kiwi, strawberries, Brussels sprouts, red and green peppers, broccoli, cooked cabbage and cauliflower. Vitamin C is perhaps the most popular supplement taken to protect against infection due to its important role in immune health.

Water: soluble vitamins have significant benefits in treatment of sepsis and septic shock, a life-threatening condition, which is caused by inflammation produced by pathogenic organisms. Other ways vitamin C aids the body are as a pro-oxidant for immune cells, antioxidant for lung epithelial cells, and immunosuppressive effects (Erol, 2020). Foods that contain vitamin C are oranges, kiwi, kale, and broccoli.

Bioavailability: Levels of vitamin C in foods depend on the growing condition, season, stage maturity, cooking practices and storage time prior to consumption.

Vitamin C is easily destroyed by heat and oxygen. Absorption levels depend on the amounts consumed. About 70-90% of vitamin c is absorbed. If intakes exceed 1000 mg/day, absorption levels drop to 50%. Sources: Fruits (especially citrus fruits like lemon, orange, amla etc.), cabbage-type vegetables, green leafy vegetables, lettuce, tomatoes, potatoes and liver.

2.2.3 Vitamin E:

Vitamin E is vital for maintaining the overall health of elderly people, including their immunity. Vitamin E is a powerful antioxidant that can protect you from various infections, bacteria, and viruses. Soaked almonds, peanut butter, sunflower seeds, and even hazelnuts should be consumed to get the daily dose of vitamin E.

Vitamin E functions primarily as an un-specific, chain-breaking antioxidant that bans the spread of lipid peroxidation. This vitamin is often a radical peroxyl scavenger that protects the polyunsaturated fats in plasma membranes and lipoproteins (Liang et al., 2003).

F2-isoprostan quantification is the most effective indices of free-radical production and oxidative lipid destruction in vivo (Lin et al., 2002).

The F2-isoprostans are enhanced, and their emission may be reduced by taking supplements with vitamin E. Vitamin E performs a significant part in preserving immune responses, with such a small deficiency effecting immunity, or supplements with rates higher than prescribed, improving elderly people's humeral and cell-mediated immunity (Mastaloudis, Leonard, & Traber, 2001).

The impact of vitamin E supplements is still not studied in sufficient aspect and equivocal on the immune and inflammatory response to sustained exercise.

Bioavailability:

Vitamin E is a fat soluble nutrient. As such, absorption of this vitamin is enhanced in the presence of fat in a meal. Individual on diets consisting mostly of starchy staples-with inconsistent intake of edible oils or other vegetables sources of Vitamin E-are at a higher risk of inadequate vitamin E intake.

Sources: Edible vegetable oils (i.e. wheat germ, sunflower and rapeseed), leafy green vegetables (spinach, chards etc.), nuts, avocados, sunflower seed, mango and kiwi fruit.

2.2.4 Vitamin B Complex:

B vitamins, including B12 and B6, are important for healthy immune response. Yet, many adults are deficient in them, which may negatively affect immune health.

2.2.5 Vitamin A:

Beta carotene gets converted to vitamin A, which is essential for a strong immune system. It works by helping antibodies respond to toxins and foreign substances.

Good sources of beta carotene include sweet potatoes, carrots, mangoes, apricots, spinach, kale, broccoli, squash and cantaloupe.

2.2.6 Zinc:

Zinc helps cells in your immune system grow and differentiate. One meta-analysis revealed that zinc supplements may shorten the duration of symptoms of the common cold (Hemila, H.et al., 2016). However, it concluded that "large high-quality trials are needed" before definitive recommendations can be made.

Sources of zinc include beans, chickpeas, lentils, tofu, fortified cereals, nuts, seeds, wheat germ, oysters (including canned), crab, lobster, beef, pork chop, dark meat poultry and yogurt. Zinc is a mineral that's commonly added to supplements and other healthcare products like lozenges that are meant to boost your immune system. This is because zinc is essential for immune system function. Zinc is needed for immune cell development and communication and plays an important role in inflammatory response. A deficiency in this nutrient significantly affects your immune system's ability to function properly, resulting in an increased risk of infection and disease, including pneumonia. Zinc deficiency affects around 2 billion people worldwide and is very common in older adults. In fact, up to 30% of older adults are considered deficient in this nutrient. Numerous studies reveal that zinc supplements may protect against respiratory tract infections like the common cold.

Bio availability: like Iron, Zinc absorption will depend on the zinc body pool, with those having poor zinc status able to absorb zinc more efficiently in the gut. Foods rich in phytate lead to previously absorbed zinc being lost in the faces. Protein may enhance absorption of Zinc.

Sources: meats, some shellfish, legumes, whole grains and some fortified cereals.

2.2.7 Magnesium:

A very vital mineral for our immune system, magnesium, is also an important electrolyte that helps our body strengthen our immune system's natural killer cells and lymphocytes. It is also a key source of energy for our cells called adenosine triphosphate (ATP), which is so crucial that without this energy, our cells cannot function properly. Magnesium helps the hemoglobin in our blood which is responsible for delivering oxygen from our lungs to the entire human body, which assists in a COVID-19 infection since the virus attacks the respiratory system (Sanderson, 2020). Foods rich in magnesium are dark chocolate, black beans, avocados, and whole grains.

2.2.8 Selenium:

Selenium is a mineral that's essential for immune health. Animal research demonstrates that selenium supplements may enhance antiviral defense against influenza strains, Including, H1N1.

Bioavailability: selenium from food sources is highly bioavailable.

Sources: Seafood, meat, whole grains, dairy, fruits and vegetables etc.

Table 2.1: Some Sources of Vitamins and Minerals

Vitamins or Minerals	Sources
Vitamin D	Eggs, Cheese, Tofu and Mushrooms
Vitamin C	Oranges, Grapefruit, Kiwi, Lemon, Strawberries, Brussels Sprouts,
B complex vitamins	Meat (Especially Liver), Seafood, Poultry, Eggs, Dairy Products, Legumes, Leafy Greens Vegetables, Seeds and Fortified Foods, Such As Breakfast Cereal and Nutritional Yeast.
Vitamin A	Sweet Potatoes, Carrots, Mangoes, Apricots, Spinach, Kale, Broccoli, Squash and Cantaloupe
Zinc	Beans, Nuts, Cereal and Seafood
Selenium	Whole grains and dairy products, including milk and yogurt, Pork, beef, turkey, chicken, fish, shellfish, and eggs.

2.2.9 Vitamin B6:

B6 is required for maintenance of homo-cysteine levels in Blood. (Raised homo-cysteine is a hazardous for cardiovascular disease). Vitamin B6, involves 3 structures pyridoxine, pyridoxal and pyridoxamine. All three types of B6 can be changed over to the co-enzyme PLP.

Vitamin B6 in its coenzyme structure is included responses and it is fair to state that vitamin B6 is required for most of biological responses in our body.

While more research is important to understood B6's role in immunity examines that Vitamin B6 inadequacy impact both hum-oral and cell mediated immune reactions and in this way disables immune reaction.

Bioavailability: if consuming a mixed diet, the bioavailability of vitamin B6 is about 75%. Vitamin B6 is destroyed by heat but it remains stable during storage.

Sources: Chicken, liver, Fish, Nuts, Chickpeas, maize and whole grain and cereals, and vegetables (especially green leafy vegetables), bananas, potatoes and other starchy vegetables.

2.2.10 Vitamin B12:

Vitamin B12 is required for appropriate red blood cell construction, nerve system capacity, and DNA combination. It cooperates with Foliate and Vitamin B6, to help support blood homo-cysteine levels, at a research point of view vitamin B12 has an important role in immune modulator for cellular immunity.

Bioavailability: while there is insufficient data on the absorption of vitamin B12, experts assume that about 50% vitamins B12 are absorbed by adults with a healthy digestive tract. Inadequate absorption occurs when there is not enough acid in the stomach or when a protein called intrinsic factors is not produced in the stomach.

Conventional cooking methods involving high heat and long cooking times may result in some vitamin B12 losses.

Sources: it Include mainly animal sources like shellfish, liver, some fish (herring, sardines, salmon, trout) milk and milk products.

2.2.11 Iron:

Iron is fundamental for the development of hemoglobin in red platelets; which transports oxygen around the body. Iron additionally serve as a cofactor to enzyme in oxidation/decrease responses (i.e., acknowledges or gives electrons). These responses are vital to cells' energy metabolism .Research recommends a low iron level affects our capacity to have a sufficient immune reaction.

It is required for immune cell production and development especially lymphocytes, which are connected to the specific reactions to infection. Iron sequestration is a significant intrinsic host defense system because numerous pathogens rely upon this fundamental component. As a result, availability of body iron is carefully controlled and bound to proteins, for example, transferring and ferreting

Bioavailability: Iron is carefully regulated by the body and absorption rates vary by the size of a person’s iron stores. Many factors affect the absorption of iron. Factors that enhance absorption of in organic iron are Vitamin C and animal protein. Factors that inhibit inorganic iron absorption include phytate, polyphenol, vegetable protein and calcium.

Source: red meat, fish, poultry, shellfish, eggs, legumes, grains, and dried fruits.

2.2.12 Medicinal Mushrooms:

Medicinal mushrooms have been used since ancient times to prevent and treat infection and disease. Many types of medicinal mushrooms have been studied for their immune-boosting potential. Over 270 recognized species of medicinal mushrooms are known to have immune-enhancing properties.

Cordyceps, lion’s mane, maitake, shitake, reishi, and turkey tail are all types that have been shown to benefit immune health. Some research demonstrates that supplementing with specific types of medicinal mushrooms may enhance immune health in several ways, as well as reduce symptoms of certain conditions, including asthma and lung infections.

Aside from the items listed above, many supplements basically from medicinal plants may help improve immune response:

a. **Astragalus:** Astragalus (Astragalus*propinquus*) is an herb commonly used in Traditional Chinese medicine (TCM). Animal research suggests that its extract may significantly improve immune-related responses.
b. **Garlic:** Garlic (Allium sativum) has powerful anti-inflammatory and antiviral properties. It has been shown to enhance immune health by stimulating protective white blood cells like NK cells and macrophages. However, human research is limited.
c. **Turmeric:** The bright yellow spice, Turmeric, contains a compound called cur-cumin, which boosts the immune function.
d. **Andrographis:** Andrographis (Andrographis paniculata) this herb contains andrographolide, a terpenoid compound found to have antiviral effects against respiratory-disease-causing viruses, including enter virus D68 and influenza A.
e. **Licorice:** Licorice (Glycerrhizaglabra) contains many substances, including glycyrrhizin that may help protect against viral infections. According to test-tube research, glycyrrhizin exhibits antiviral activity against severe acute respiratory-syndrome-related corona virus (SARS-CoV).
f. **Pelargonium Sidoides:** Some human research supports the use of this plant's extract for alleviating symptoms of acute viral respiratory infections, including the common cold and bronchitis. Still, results are mixed, and more research is needed.
g. **Curcumin:** Curcumin is the main active compound in turmeric. It has powerful anti-inflammatory properties, and animal studies indicate that it may help improve immune function.
h. **Echinacea:** Echinacea is a genus of plants in the daisy family. Certain species have been shown to improve immune health and may have antiviral effects against several respiratory viruses, including syncytial virus and rhinoviruses.
i. **Propolis:** Propolis is a resin-like material produced by honeybees for use as a sealant in hives. Though it has imprerespiratory immune-enhancing effects and may have antiviral properties as well, more human research is needed.

Elderberry:

Elderberries are full of nutrients including minerals like phosphorus, potassium, iron, copper and vitamins, such as vitamin A, B, and C, proteins and dietary fiber. Elderberries have antibacterial and antiviral qualities which help fight cold and influenza.

2.2.13 Antioxidants:

Glutathione is a powerful antioxidant in the body, it scavenges damaging free radicals and is involved in tissue repair and builds chemicals and proteins that are used for the immune system. N-Acetylcysteine, or NAC, promotes the production of glutathione and is also used as a supplement.

Studies in animal models of other viral infections have shown that NAC reduced the severity and duration of symptoms by increasing cellular defense and repair.

NAC is taken in doses of 500-600 mg. Glutathione can be taken orally 500 mg or by IV 400–2400 mg with a doctor's order.

Quercetin is a bioflavonoid found in a variety of fruits and vegetables. Animal and laboratory studies have demonstrated that Quercetin can inhibit a wide range of virus infections including a COVID-19-related corona virus SARS CoV. Quercetin supports antioxidant capacity and protects lung tissue.

As a supplement is combined with vitamin C, brome lain is sold as a single supplement. Recommendation is between 500 and 1000 mg daily (Center and fees, 2020).

Major sources are leafy green vegetables, dill, peppers, apples, grapes, fennel leaf, red onion, oregano, chili pepper, green tea, and black tea.

2.3 Remedies for Immunity Boosting:

a. Amla or Indian Gooseberry: It is a powerhouse of nutrition and is matchless in its power to boost the body's immunity. Have half a teaspoon of crushed fresh amla with one crushed garlic clove on an empty stomach.
b. Immunity Balls: Take one teaspoon powdered turmeric, one tablespoon jaggery, one tablespoon cow ghee, and one tablespoon dry ginger powder. Mix well and make into small round balls. Have 2-3 daily.
c. Turmeric Milk: Half tea spoon Haldi (turmeric) powder in 150 ml hot milk-once or twice a day.
d. Ghee: Ghee (clarified butter), Sesame oil, or Coconut oil in both the nostrils to keep the nostrils clean.
e. Herbal Tea: herbal tea or decoction of Holy basil, Cinnamon, Black pepper, Dry Ginger and Raisin.
f. Tulsi-Peppercorn: Begin your day with home grown tulsi leaves along with organic honey and freshly crushed peppercorn. Take 5-7 leaves, add two crushed peppercorns with one teaspoon honey and consume immediately on an empty stomach and do not drink water after this.
g. Orange Juice with Pepper: Drink a glass of fresh orange juice daily to which a pinch of pepper has been added. It is loaded with antioxidants and is a rich source of Vitamin C. It will naturally help in boosting your immunity.
h. Ginger-Tulsi: All you need to do is, take juice of fresh ginger, and crush some tulsi leaves in it. Add a teaspoon of honey to it. Consume it daily to get relief from cough and increase the body immunity.
i. Kadha: Make a warm tea with few tulsi leaves, a piece of ginger and a dash of black pepper. All these ingredients play an important role in fighting illness-causing bacteria and increase the body's immunity.
j. Tender Neem Leaves: Traditionally in India, tender neem leaves were consumed by people on an empty stomach and it was believed to be a potent blood purifier. It has antiviral and anti-bacterial properties and is believed to increase the body's immunity.

Some other remedies are Kalonji oil, Elderberry, Astragalus, Andrographis, Curcumin, Echinacea, Propolis, and Quercetin.

Also, there are many products formulations are available in market for Immunity Boosting like Gilroy Ghanvati, Vitamin C capsules, Amla juice etc.

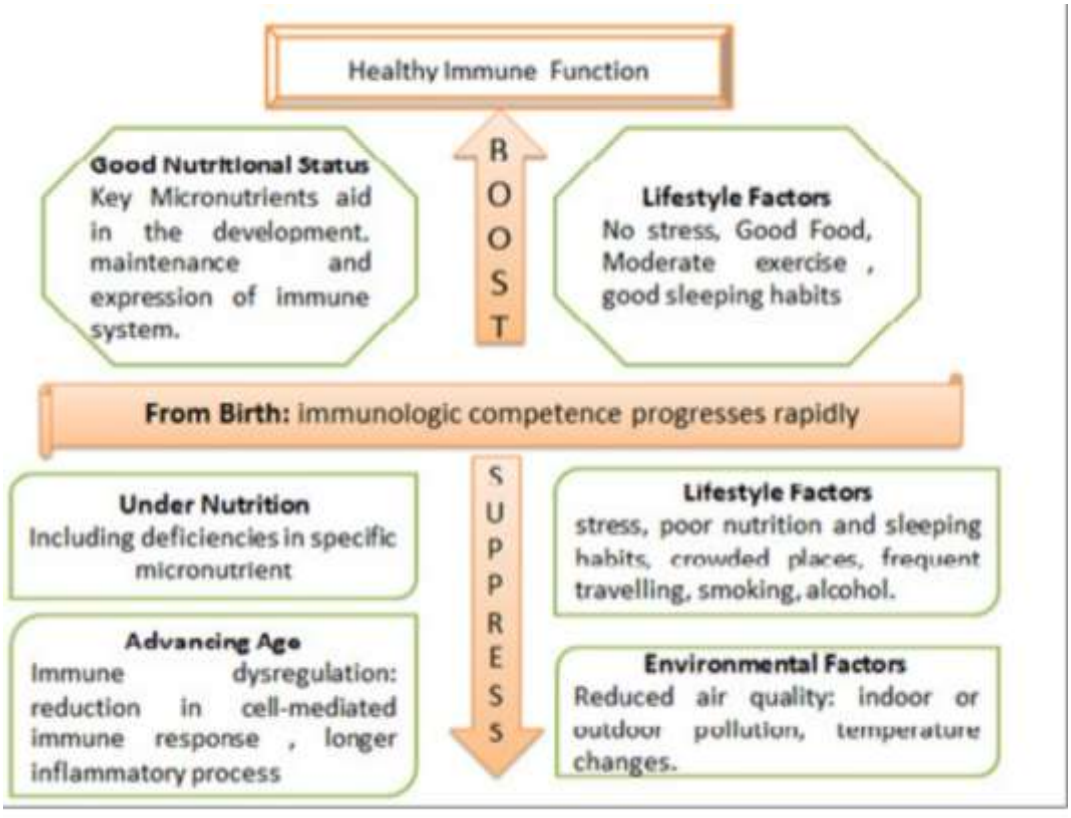

Figure 2.4: Factors Affecting Immune System

Apart from above supplements, Protein is a key building block for immune cells and antibodies and plays a crucial role in helping our immune system do its job. Protein comes from both animal and plant-based sources and includes fish, poultry, beef, milk, yogurt, eggs and cottage cheese, as well as nuts, seeds, beans and lentils.

Probiotics and prebiotics also boost the health of the micro biome, which in turn supports our immune system. Sources of probiotics include fermented dairy foods such as yogurt and kefir, and aged cheeses, as well as fermented foods such as kimchi, sauerkraut, miso, and tempeh and sourdough bread. Sources of prebiotics include whole grains, bananas, onions, garlic, leeks, asparagus, artichokes and beans. Apart from maintaining a healthy lifestyle, includes immunity booster in diet i.e. taking supplements, the Indian health ministry is also suggesting few organic and natural ways to practice as preventive measures to fight COVID-19.

The Ministry of AYUSH has recommended the following self-care guidelines as preventive measures and to boost immunity with special reference to respiratory health.

a. Drink warm water throughout the day.
b. Practice Meditation, Yogasana, and Pranayama.
c. Increase the intake of Turmeric, Cumin, Coriander and garlic.

d. Drink herbal tea or decoction of Holy basil, Cinnamon, Black pepper, Dry Ginger and Raisin.
e. Avoid sugar and replace it with jaggery if needed.
f. Apply Ghee (clarified butter), Sesame oil, or Coconut oil in both the nostrils to keep the nostrils clean.
g. Inhale steam with Mint leaves and Caraway seeds.

2.4 Some Other Activities to Do For Immunity-Boosting Other Than Healthy Diet:

Don't Compromise on Sleep: Good snooze time for 7-8 hours is the best way to help your body build immunity; lesser sleep will leave you tired and impair your brain activity. The lack of sleep will prevent the body from resting and this will impair other bodily functions that will have a direct impact on your immunity. Lack of sleep adversely affects the action of the flu vaccine. Stay Hydrated: Drink up to 8-10 glasses of water every day, to stay hydrated. Hydration will help flush out the toxins from the body and lower the chances of flu. Other alternatives include juices made of citrus fruits and coconut water, to beat the heat.

Don't Skip on Exercise: A good diet should be followed by an exercise routine. Remember to exercise regularly; even light exercise will go a long way in releasing the toxins from your body. It is recommended to exercise for 30 to 45 minutes, depending on your stamina.

If you have not started exercising yet, then it is a good time to start. There are several YouTube channels and apps to help you exercise at home. Regular exercise improves metabolism, which has a direct correlation with body immunity.

Distress Yourself: These are testing times, and a prolonged period of staying indoors has its implications on your mental wellbeing. The growing anxiety around the pandemic is another concern that is affecting millions across the globe. While the uncertainty might be overwhelming, there are few steps we can follow regularly to help relieve our stress, stress is known to have an adverse effect on immunity.

Practice meditation: Too much stress releases the hormone known as cortisol, which impairs your response to immediate surroundings and makes your body susceptible to infections; you are left feeling constantly anxious. The best way to relieve stress is through meditation, it is a tried and tested activity to calm the nerves. If you need help meditating, then there are several channels on YouTube that have instructional resources to help you meditate.

2.4.1 Avoid Smoking, Alcohol and Other Addictive Substances:

Certain habits like smoking, vaping, alcohol consumption and substance abuse have a direct correlation between weakened body defenses and respiratory illnesses. Engaging in smoking and vaping is proven to weaken your lung capacity and destroy the cells lining your respiratory tracts, these cells are crucial to fight viruses that enter through your nasal orifices.

There is new research claiming that individuals who engage in heavy alcohol consumption tend to suffer from ARDS (Acute Respiratory distress syndrome) which is one of the conditions caused by Covid 19 infection. Practice moderation, if you are dependent on any of these, as sudden withdrawal can also prove to be risky.

Travelling: Avoid all kinds of non-essential travels. Most Covid 19 positive cases are imported cases, which later spread to the communities. Avoid being exposed to the public transport system and public places to avoid any likelihood of exposure. In case you have to travel, make sure to cover your nose and mouth with a mask and carry an alcohol-based hand sanitizer, at all times.

Remember to sanitize each time you touch a surface, as Covid 19 strain can stay on surfaces for a few hours to days. Use your non-dominant hand while accessing the doorknobs and handles, as these are frequently touched by many people.

Lifestyle: Stress negatively alters the immune system responses within the body (Salleh, 2008). Stepping away from the media and TV is also very important in letting one's mind distress from the world a bit. Try limiting yourself to about an hour in the morning and at night to just catch up and see if there are any important changes.

Sleep, a huge influence on the immune system, gives the body an opportunity to heal and rest, especially in critical illnesses (Kamdar, Needham, & Collop, 2012). Furthermore, sleep was considered extremely important by doctors in the recovery of their patients during the Spanish Flu Pandemic.

Exercising helps raise the levels of white blood cells and antibodies that fight off infections (Join & Calendar, 2020). Exercise is especially important after a critical illness to improve muscle mass, strength, and resiliency (Heyland et al., 2016). Exercise can also help with the prevention of blood clots, which have been a symptom for some people who contracted COVID-19.

Eating a well-balanced, healthy diet and staying away from processed junk food is very important to maintain overall health, as well as to support immune functions. Eat as much fresh produce as possible, but if it is not in season or hard to find then the next best thing is fermented or frozen. These items are normally picked at the peak of the season and then frozen or fermented straight away (Join & Calendar, 2020), also, make sure to eat sufficient protein (Hyman, 2020).

While the battle against the Covid-19 pandemic is fought by our health care workers, we can do our bit by limiting our exposure to the virus by staying indoors, social distancing, eating healthy, hydrating and following basic hygiene protocol.

2.5 Conclusion:

Great nutrition is central to improving immunity. The immune system is the body's protection against disease and virus and it has long been studied that few variables impact the capacity of the immune system including stress and nutrition.

Vitamins and minerals, known as micronutrients, are supplements required by our body for ideal function and frequently required in just limited quantities. These micronutrients are not delivered in the body and in this way should be acquired from our food. Many researches show the key role nutrition plays in powerful working of our immune system. Giving a diet high in nutritious food rich in vitamins and minerals supports ideal capacity of the immune system by giving cancer prevention agents to slow harm of cells brought about by free radicals or aiding T-cell creation.

Although, there is no information concerning nutritional components according to the hazard and seriousness of viral disease, such as, COVID-19 the role of nutrition in immunity has been established. The European Journal of Clinical Nutrition concluded that without satisfactory nutrition, the immune system is clearly deprived of the components expected to create a successful immune reaction. Great nutrition is in this way significant in supporting an ideal immune system which can lessen the danger of viral diseases.

Vitamin C, vitamin D and zinc have immune improving and immune regulating properties and assume synergistic role in supporting parts of both innate and adaptive immunity which contain epithelial obstructions, cell resistance and antibodies comprising the three primary lines of resistant protection.

Then again, lacks of vitamin C, vitamin D and of zinc seriously discourage immune reactions and lead to an expanded hazard for infection for model in the respiratory tract. Micronutrients are accepted to work all things considered to help an ideal immune system. Based on a variety of systematic and clinical information, vitamin A, B, C, D, E, foliate, zinc, iron, copper, and selenium are especially imperative to boosting immune response.

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3. Invisible yet Invulnerable Asymptomatic Covid-19

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3.1 Summary:

The world is running on through a microbiological war, named Covid 19, which causative agent is SARS CoV-2. Till now this enemy killed a lot of people and many doctors, nurses, health workers and also police sacrificed their lives to make the human beings winner in this war but corona virus is continue changing its genetic characteristics by which it becomes uncontrollable to human beings.

Though vaccination has been started but the new Covid related problem is a symptomatic infection, that means the person is infected but not feeling and expressing any symptoms of Covid infection but he/ she is already spreading the virus.

These people can be detected as Covid positive only by clinical test. The main cause of a symptomatic Covid infection is that the novel Corona virus can hide its genome for being unrecognizable. And some other minor causes for a symptomatic infection are T-cell memory, immunity from childhood vaccination, biology and wear masks. By which virus infected people but not become severe in most of the cases and some cases it becomes critical and cause death.

3.2 Introduction:

Covid 19 is an ongoing microbial storm through all over the world that has already snatched a lot of lives and now also on its way of snatching. This pandemic causing Corona virus was 1st identified in December, 2019 at Wuhan and on 11th February, 2020 it was officially named "Severe Acute Respiratory Syndrome Coronavirus-2" or "SARS CoV-2" by 'International Committee on Taxonomy of Virus'.

Then SARS CoV-2 started its fatality in many countries and in India it started its divesting storm from March and continued it till September, 2020 which is named as the '1st wave of Covid'. Then the peak value of graph became slow down and was running in this way with maintaining this position but in February, 2021 SARS CoV-2 has started again its furious job that is now going on, named as the '2nd wave of Covid' and in the 2nd wave mainly India has been affected very much and due to scientific research works the 3rd wave of Covid can be appeared in about September, 2021.

Till now the worldwide Covid positive case is 17.8 Cr among which number of death case is 38.6L. In this case United States is on the top position and India is in the second position.

The symptoms by which normally a person is detected as Covid positive, are including cough, fever, fatigue, shortness in breathing, headache and smell problem and in the severe cases the symptoms are including pneumonia and heavy breathing problems with too much body pain.

But in the 2nd wave in many cases it is observed that there is no symptom of Covid infection on the victim but he/she is Covid positive. That is called Asymptomatic Infection. That means the asymptomatic Covid cases are laboratory confirmed cases, not detected by physically signs and this cases are very harmful for spreading the causative pathogen Corona virus.

The again and again researchers revealed that approx. 20% people carry out no symptoms those are tested positive for the infection of new corona virus.

Clinically assigned mild cases are patients with upper respiratory tract symptoms (&/ or fever) without shortness of breath and having oxygen saturation at room air of more than 94%.

3.2.1 Asymptomatic Infection:

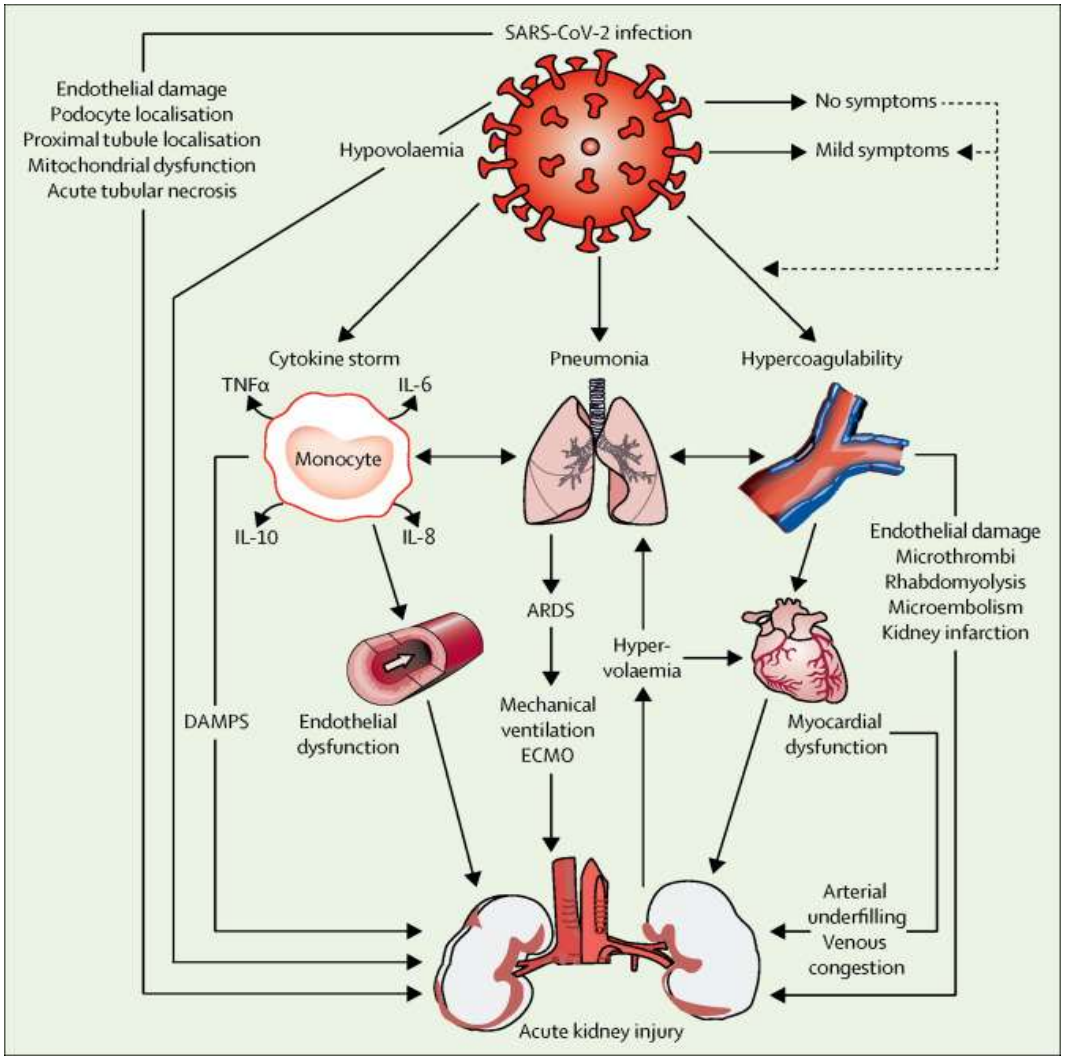
Asymptomatic infection means an infection that is only confirmed by clinical tests because the infected person does not carry out any symptoms or physical features of that particular disease.

It is also called as pre-infection or in apparent infection. Most young and healthy people may be infected but likely asymptomatic. However, some healthy people became very ill and some died. In terms of percentage it seems very low, but the chance is not zero. Asymptomatic patients carry a lot of viruses in their body.

Recently, from several studies scientists have observed that there are a huge asymptomatic Covid cases. The amount of viral load is same among asymptomatic patients and symptomatic patients.

Researchers at the Center for DNA Fingerprinting and Diagnostics (CDFD) in Hyderabad suggested examining asymptomatic primary and secondary communications, which need to be monitored in India's fight against the corona virus.

In addition to this study, even recent studies in South Korea have shown that asymptomatic and symptomatic people carry a similar viral load on their bodies, the amount of virus in the throat and nose indicating that asymptomatic people can spread the corona virus just as much as symptomatic.



Recently, Indian scientists have observed a higher association between asymptomatic COVID-19 cases and viral load, or the amount of virus in an infected person's bodily fluid, in a study of over 200 patients with SARS-CoV-2 virus in Telangana. The researchers, including those from the Centre for DNA

Fingerprinting and Diagnostics (CDFD) in Hyderabad, advise testing asymptomatic primary and secondary contacts followed by surveillance as now an essential thing in India's fight against Corona virus.

Apart from this study, even a recent study from South Korea found that asymptomatic and symptomatic people carry a similar viral load in their bodies, which is the amount of virus located in throats and noses that indicates asymptomatic people could potentially spread the Corona virus just as readily as those with symptoms.

3.2.2 Pathogenesis:

Like SAR-CoV, SARS-CoV-2 used Angiotensin-converting enzyme 2 (ACE 2) as its receptor to attack cells. ACE2-mediated Angiotensin II (Ang II) plays an important role in the causing of severe lung failure after invasion by the degenerative virus. The level of transmission of the virus depends on the maturity and binding capacity of ACE2.

Therefore, low levels of ACE2 or its weak binding ability to SARS-CoV-2 should be a major factor that leads to infectious infections. It has been studied that only a specific mild immune response occurs in asymptomatic patients by SARS-CoV-2 attack.

However more clinical samples should be collected, and a relative test of ACE 2 should be performed and different types of COVID-19 cases should be compared. This would be a more effective way to explain its pathogenesis.

3.2.3 Cause of Asymptomatic Covid Infections:

In our lungs there is a special type of immune cell, named as Alveolar Macrophages that functions in the maintenance of health environment in lungs. As the alveolar macrophages present in lungs in huge amount, it's the 1st cell type that invade virus encounter.

When our body able to identify a viral infection, then and there our immune system starts to produce interferon's which is a group of cytokines that function in immune response to fight against the viral infection. Not only in case of Covid infection but the alveolar macrophages also produce interferons in case of influenza that is already previously shown.

As SARS CoV-2 causes respiratory syndromes. It normally starts infection from the parietal pleura layer of lungs. Some recent studies reveal that the interferon production in the viral infected cells. It causes in the lower productivity of interferon's and allows the immune system to play its role but with limited activity. As these parietal pleura are the main target of infection of the virus particles, it must be taken up as the main cell type for viral attack.

The most effective cause of asymptomatic Covid infection is the again and again mutation of corona virus, and as a result the SARS-CoV-2 virus become able to hide its genome from being unrecognized. The results of researches show that alveolar macrophages effectively produce interferons when infected with known viruses, such as influenza. It becomes also confirmed that the alveolar macrophages have the potential to produce large amounts of interferons during a viral infection.

Therefore all of these results suggest that the SARS-CoV-2 virus may hide its genomic material from being recognized in the alveolar macrophages, thereby not inducing the production of interferons. That is why there will be no activation of the immune system in the early stages of a SARS-CoV-2 infection, allowing the virus to spread further in the community before symptoms occur.

The results of research reveal that when the infection is caused by a known virus the alveolar macrophages start interferon production with high efficiency and rapidity –

3.2.4 T-Cell Memory:

For the 'memory' T-cells, i.e., the white blood cells somebody have partial immunity against the corona virus T cells control the immune system by recognizing the invaders. Where they made a comparative examination by taking blood samples from the Covid 19 recovering persons and the unaffected persons who donated blood between 2015 to 2018. Due to their research studies in the old samples' the T-cells come forward to identify the novel corona virus in 40% to 60%.

This partial immunity appears for the previous infection of corona virus that cause common cold. And according to the research studies immune response is against the spike proteins of corona virus to destroy cells.

3.2.5 Immunity from Childhood Vaccination:

Some research studies suggest that the childhood vaccines can supply the partial immune against the novel corona virus infection in case of some patients. Researchers found that seven types of childhood vaccines—administered one, two, or five years previously—were associated with having a lower infection rate from the corona virus.

This was especially true among people who recently received a pneumonia vaccine, which was associated with a 28% reduction in corona virus-infection risk, and polio vaccines, which were associated with a 43% reduction in corona virus-infection risk. And those associations held even after adjusting for a variety of factors, including geographic incidence of the virus, demographics, and underlying conditions.

3.2.6 Biology:

Due to some research study ACE2 receptors may affect the severity of illness a person develops from the new corona virus. According to Cha, the corona virus can be caught onto ACE2 receptors, which in healthy people keep blood pressure stable, then travel through the body and replicate. Researchers are intrigued by the receptors because they've theorized that minimizing those receptors may obstruct the virus' ability to replicate or "trick the virus into attaching itself to a drug" instead, so it's not able to replicate and travel through the body.

3.2.7 Mask:

In the asymptomatic infection of SARS CoV-2 the wide spreader use of mask has a role. Due to some survey and research works researchers found that different asymptomatic case numbers were on two different cruise ships. On the Diamond Princess, where masks weren't used, 47% of those infected with the virus were asymptomatic.

But on an Argentine cruise ship, where all passengers were given surgical masks and crew received N95s, 81% of cases were asymptomatic. In some early corona virus outbreaks where people weren't wearing masks, 15% of those infected were asymptomatic.

However, later in the pandemic, when more people were wearing masks, asymptomatic rates jumped between 40% and 45%.

3.3 Classifications of People Based on the Severity of the Disease Symptoms:

The symptoms may shift from mild to moderate symptoms or vice-versa during the course of illness. With so many people that are affected, everyone may not fit perfectly into the simple groups of classification.

If the symptoms are predominantly mild, with one or two moderate symptoms, he/she may be classified as one with mild to moderate symptoms. People with COVID-19 are classified broadly as follows:

a. Silent carriers
b. Patients with mild to moderate symptoms
c. Patients with moderate to severe symptoms
d. Critically ill patients with multi-organ dysfunction.

Asymptomatic /Presymptomatic	Positive for SARS-CoV-2 using a test but no symptoms that are consistent with COVID-19
Mild Illness	Signs and symptoms of COVID-19 but no shortness of breath, dyspnea, or abnormal chest imaging
Moderate Illness	Signs and symptoms of lower respiratory disease or abnormal imaging and $SpO_2 \geq 94\%$ on room air at sea level
Severe Illness	$SpO_2 < 94\%$ on room air at sea level, PaO_2/FiO_2 <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%
Critical Illness	Respiratory failure, septic shock, and/or multiple organ dysfunction

3.3.1 Silent Carrier:

These silent carriers or spreaders are those people who are infected with corona virus but show little or no symptoms of the disease. As a result, these people carry on with their daily lives, meeting family and friends, going to work, and spreading the disease without their own knowledge.

It appears that most asymptomatic carriers are healthy young adults and children. If person come to contact with people who are positive for Covid-19, he/ she may be positive but not showing any symptoms of the disease.

Types of Silent Carriers:

The terminologies, used for classifying the silent carriers are:

a. Mildly Symptomatic Carriers:

People who display very mild symptoms like a mild cough or may just be feeling a little low come in this category. The virus mainly affects the upper respiratory tract and may cause mild cough or mild breathlessness on exertion. His fever may not reach 37.8℃, lose sense of smell, have mild headaches, or develop a runny nose. These symptoms usually last for seven to ten days. It has been seen that some people showing mild symptoms can rapidly deteriorate, more often among people in the high-risk group.

b. Pre-Symptomatic Carriers:

Some people do not develop any symptoms for up to a week after contracting the disease. They may later on experience cough, fever, or breathing difficulty.

c. Asymptomatic Carriers:

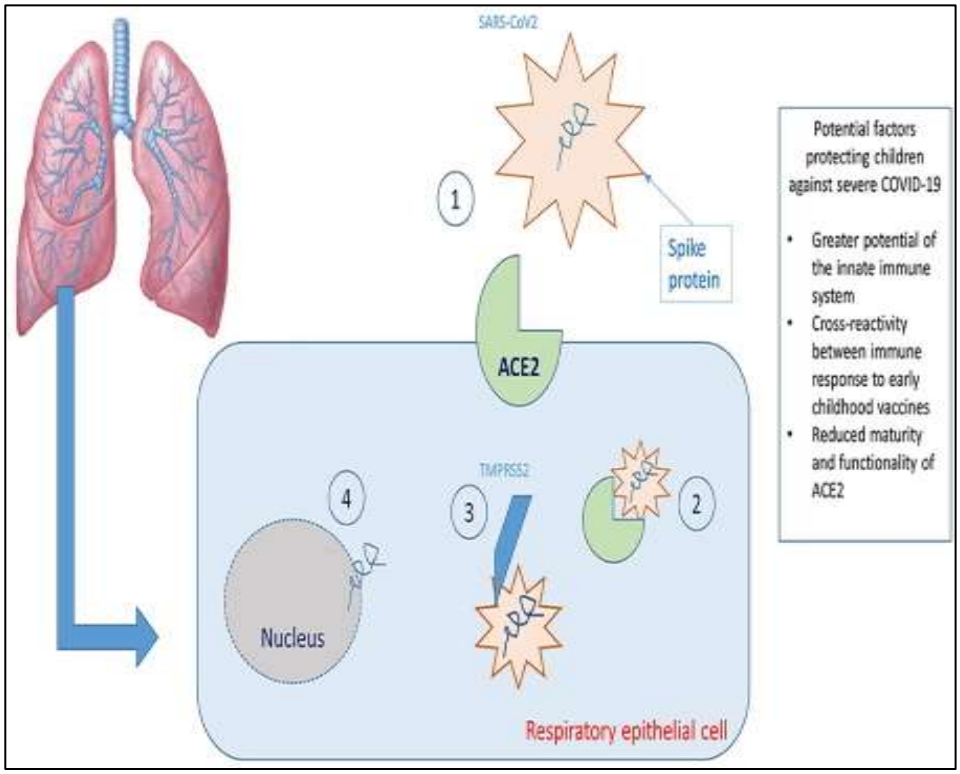
These are people who show no signs or symptoms of infection for the entire duration of the incubation period. It can last about 14 days. As a result, they spread the virus to large numbers of people. It fuels the epidemic in a quick and dangerous way.

3.3.2 Unusual Symptoms:

Some people may develop symptoms that are not typical to COVID-19. These include symptoms such as loss of smell, loss of taste, and diarrhea. This means that some of the people placed in the category of asymptomatic carriers could be shifted to the mildly symptomatic category keeping these symptoms in mind. Until these symptoms have been categorized, it is best to follow strict personal hygiene practices and Government protocols for quarantine and lockdown.

3.3.3 Children May Be Silent Carrier Of Covid 19:

New research has suggested that children may be carrier of Covid 19 disease even if they never show any symptoms. In asymptomatic condition also children carries more contagious and higher load of virus. Greater the load of virus greater will be the chance of transmission of disease. Children infected with SARS-CoV-2 may have many of these shows symptomless infection, or may have only a few symptoms, such as upper respiratory distress or gastrointestinal symptoms, or asymptomatic. The most common symptoms in children are cough and / or fever. Signs and symptoms of Covid-19 in children are similar to other infections such as influenza, streptococcal pharyngitis, and allergic rhinitis. The lack of specificity of the signs or symptoms and the significant proportion of asymptomatic infections make the development of symptom-based screening for SARS-CoV-2 detection in children may quite challenging.



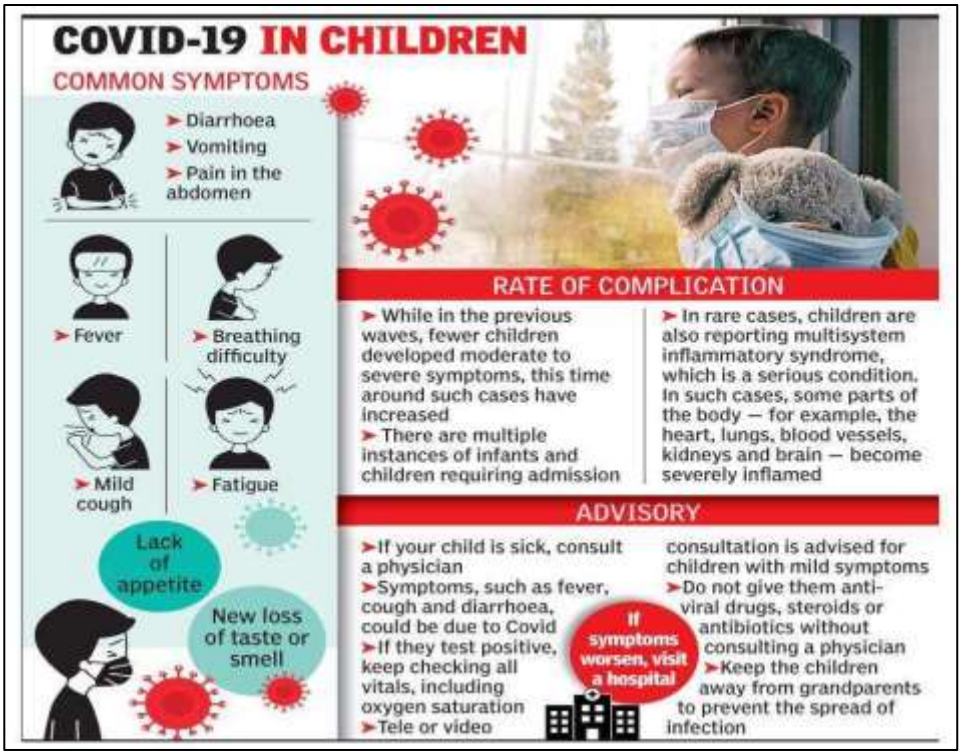


Figure 3.1: Instructions for the Patient:

a. Patients must isolate himself from other household members by staying in an identified room and keep distance mainly from the co-morbid patients those have hypertension, cardiovascular disease etc.
b. Patients must have to use mask for all time and should leave it after using 8 hours and also when he/she becomes wet. All time the patient should use N95 mask.
c. Patient should at all times use triple layer medical mask. Discard mask after 8 hours of use or earlier if they become wet or visibly soiled. In the event of care giver entering the room, both care giver and patient may consider using N 95 mask.
d. After disinfecting with 1% sodium hypochlorite ask should be left.
e. For maintaining adequate hydration in body the patient must have to drink sufficient amount of water and hydrated foods.
f. Every time try to follow the respiratory protocols.
g. Frequently wash hands with hand wash during 40sec and sanitize with alcoholic sanitizers.
h. Avoid shearing of personal things to others in the house.
i. All time try to clean the surfaces with 1% sodium hypochlorite which are in touch of the Covid patient.
j. Self-monitoring of blood oxygen saturation with a pulse oximeter is strongly advised.
k. The patient will self-monitor his/her health with daily temperature monitoring and report promptly if any deterioration of symptom as given below is noticed.

3.4 Treatment for Patients with Mild/ Asymptomatic Disease in Home Isolation:

a. Patients must in contact with a treating physician and report any deterioration immediately.
b. Continue medications for other co-morbidities after consulting with the treating physician.
c. Follow-up of patients for fever, runny nose and cough as warranted.
d. Patients can take hot water gargle or steam inhalations twice a day.
e. If fever is not controlled with the maximum dose of tablet. Patients can have Paracetamol 650 mg four times a day, consult a treating physician who may consider prescribing non-steroidal anti-inflammatory drugs (NSAIDs) as other drugs (for example: tab naproxen 250 mg twice a day).
f. Consider tablet Ivermectin (200 mcg / kg once a day on an empty stomach) for 3 to 5 days.

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4. Molecular Biology of SARS-CoV-2

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4.1 Introduction:

Coronaviruses (CoV), belong to the Nidovirales order has been associated with a broad spectrum of diseases in animals and humans. First recognized by scientists in 1968, coronaviruses (CoVs) are among the largest family of viruses currently known. These viruses are enveloped and possess (+)-single stranded RNA as its genetic material. Human coronaviruses (HCoVs) are known to cause enteric/respiratory infections. The main HCoV is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for COVID-19 pandemic, activate an excessive immune response called as a cytokine storm, cause acute respiratory distress syndrome (ARDS), multi-organ failure, and death with 2% mortality rate. Observations in people with COVID-19 suggest that the virus can be carried in the blood and infect various organs or tissues.

COVID-19 first emerged in December 2019, when a cluster of patients with pneumonia of unknown cause was recognized in Wuhan, China. As of July 15, 2021, in India, the number of identified cases of SARS-CoV-2 is 3,10,26,829 with 4,12,531 confirmed deaths. The outbreak of SARS- CoV-2 pandemic has made its extraordinary global, societal and economic troublemaking impact on human population.

4.2 Structure:

CoVs are the largest known RNA viruses, with a genomic size of about 30 kb. Their genome is monopartite, ss RNA of positive polarity, modified with a 5'-cap, and 3'-poly (A) tail that can be translated upon entry into the host cell.

The genes that code for the five important structural proteins (the spike (S) protein, the nucleocapsid (N) protein), the hemagglutinin-esterase (HE, present in some β-coro-naviruses) the membrane (M) protein and the envelope (E) protein) occupy less about 30 % of the genome at the 3'-end. The remaining 60 -70 % of the genome is occupied by a single gene that codes for the viral replicase/transcriptase proteins.

The virions are spherical or pleomorphic enveloped particles with a diameter of 80-120 nm, formed by the structural proteins. The S glycoprotein (150 kD with 1300 amino acid residues) with a club-like structure is a large type I transmembrane polypeptide having a N-terminal exodomain and a C-terminal endodomain that assembles into trimeric spikes that project from the virus and this whole structure is involved in receptor binding and membrane fusion.

Another major protein of the viral envelope is M (about 30 kD with approximately 235 amino acid residues) which is a type III transmembrane glycoprotein which is crucial for the shape of the virus, N-terminal and C-terminal are ecto and endodomains respectively. The endodmain binds with RNA of the virus. This protein shows structural resemblance with M protein of MERS and SARS and with prokaryotic sugar transport protein (Braakman and Van Anken 2000). The antigenic role of this protein is attributed to N-linked and O-linked glycosylation (Braakman and Van Anken, 2000).

The E protein (about 10 kD with approximately 100 amino acid residues) is a small transmembrane, hydrophobic protein present in lower copy numbers acts a key structural component of viral envelope. Further, this protein functions as ion channel, viroporin activity and virus assembling (Schoeman and Fielding 2019). The proline residue present in C-terminal (CT) region is highly conserved and is essential for the maturation of the protein in the Golgi of the host cell (Tseng et al., 2014). The important region in CT is PDZ-binding motif (PBM) that is crucial for cell signalling and pathogenicity. The PBM is highly conserved among SARS-CoV-2 variants and is responsible for stimulating cytokine storm, inflammasome and oedema in lungs. Key post-translational changes that occur in Eprotein are glycosylation, palmitoylation, myristoylation, and ubiquitination, (Schoeman and Fielding, 2019). Because of the functional diversity, the inhibitors of this E- protein are suitable agents for SARS-CoV-2 treatment (Alam et al. 2020).

The viral envelope surrounds a nucleocapsid with helical symmetry, which is not characteristic for positive-strand RNA viruses but rather typical of negative-strand RNA viruses. The helical nucleocapsid is formed by the N phosphoprotein, which associates with the RNA genome in a beads-on-a-string fashion. The HE (hemagglutinin-esterase) is the fourth protein constituent of the viral envelope. It forms shorter dimeric projections with C-endo and N-exo terminals. It has acetylesterase and haemagglutinating properties and may participate during cell entry and egress. The mature protein is stabilized by disulfide bonds (Liu et al., 2014), promotes reversible attachment of the virus to the host cell and acts as receptor-destroying enzyme (RDE) and as lectin.

The N-protein (43-48 kD) is ribonucleo protein rich in positively charged amino acids (lysine and arginine) is tightly bound with negatively charged RNA via N-terminal domain in a beads-on-a-string manner. N protein dimer possesses the shape of a rectangular slab in which the four-stranded β-sheet is on one side of the face and the α-helices form the opposite face of the slab (McBride et al., 2014). The protein is dimerized via C-terminal which is abundant in serine and arginine that undergo phosphorylation (Kumar et al. 2020). The reason for phosphorylation is not clearly known till date. N protein plays important role in regulation of transcription and packaging of viral genome in the formation of viable virion. The protein contains three important regions, viz. C-terminal domain (CTD), the linker region (LKR) and N-terminal domain (NTD).

Among the three, LKR can directly interact with RNA under in vitro conditions. The LKR can also bind with M protein, heterogenous nucler ribonucleoprotein A1 (hnRNPA1) and helps with the tight binding of N protein with RNA genome (McBride et al. 2014). N protein could arrest the cell cycle of host cell in G2/M phase (Wurm et al. 2001) and as it shows less variation than other envelope proteins it is considered as a vaccine candidate for SARS-CoV-2 (Ahmed et al. 2020).

A. Non-Structural Proteins:

The ribosomes of the host cell translate the viral genome in a cap-dependent mechanism produce two large polyproteins, pp1a and pp1ab. Cotranslational and autoproteolytic processing of pp1a and pp1ab result in the production of 15 or 16 nonstructural proteins (nsp) (Table 1). From pp1a, Nsp1 to nsp11 and from pp1ab nsp12 to nsp16 are produced. These sixteen nsps contribute to transcription and replication.

Table 4.1: Characteristics of non structural proteins

Name of the protein	Structural features	Functions
nsp1	180 amino acids; subjected to numerous point mutations causing variants	Degradation of host mRNA and 40s ribosomal subunit resulting in inhibition of host gene expression and cell division (Kamitani et al., 2009).
nsp2	61 amino acids; 65 kD	Interaction with nsp8; essential for the structure of double membrane vesicle (DMV)-anchored replication-transcription complexes (RTCs); promotion of cell death pathways and inhibition of cell differentiation; coding gene is essential role for RT-PCR assay
nsp3	~200 kD; ubiquitin-like domains 1 and 2 (Ubl1 and 2), Glu-rich acidic domain, macrodomain, papain-likeprotease2 (PL2pro), nsp3 ecto domain, Y1 domain and two conserved transmembrane (TM1 and TM2) domains (Lei et al., 2018)	Disruption of the host cell cycle (Ma-Lauer et al., 2016); critical role in the formation of Replication-Transcription Complex (RTC) and suppression of host immune response
nsp4	Contains four TMDs (TM1–TM4)	Key roles in the development, arrangement, and function of viral replication complexes; necessary for the structure of RTCs anchored with double membrane vesicles (DMV)
nsp5	306 amino acids	Acts as main protease and plays important role in individual viral protein synthesis; inhibition of interferon I signalling via NF-kB and STAT 1 transcription factor
nsp6	Forms complex nsp 3 and nsp4	Induction of cell autophagosis; nsp3 and nsp4, can close the DMVs
nsp7	10 kD	Co-factor component; forms heterodimer with nsp8; stabilization of RNA binding site in nsp12

Name of the protein	Structural features	Functions
nsp8	22 kD; N-terminal interacts with nsp7	Possesses RNA dependent RNA polymerase (RdRp) replicase; essential for nsp12 polymerization activity
nsp9	198 amino acids	Essential for RNA replication; requires nsp8 for its function
nsp10	148 amino acids containing two zinc finger domains	Replication regulator; interacts with nsp 14 and nsp16
nsp11	13 amino acids	endo-ribonuclease activity; inhibitory effects on TNF-α development and IL1 signaling (He et al., 2015) main roles in DNA replication, cell cycle and signalling, modification of histones, proteasomal degradation
nsp12	932 amino acids	Possesses primer-dependent and primer-independent RdRp and nucleotidyltransferase activities; enhances the helicase activity of nsp13
nsp13	Has several domains, such as NT Cys/His-rich domain (CH) with three zinc atoms and β-barrel domain	Helicase activity; hydrolyzes all forms of NTPs
Nsp14	527 amino acids	Exonuclease (3'→5') activity; interacts with nsp 10; involved in synthesis of 5' cap
Nsp15	345 amino acids	Endoribonuclease activity specific at 3'U residues; can delay interferon signalling
Nsp16	298 amino acids	nsp16 requires an interaction with nsp10 to perform powerful methyltransferase, which can transform cap-0 (7MeGpppN) specifically into the cap-1 structure; affects the immune system and activates the antiviral response in the body; interferes with interferon β and Interferon Stimulated Response Element (ISRE) signalling

4.3 Multiplication Cycle:

Attachment and entry of SARS-CoV-2 into host cell:

The binding and entry of SARS-CoV-2 into the host-cell depend on the viral S glycoprotein, comprised of two domains S1 and S2. The vastly variable S1-RBD domain (receptor binding domain) recognizes and binds with angiotensin-converting enzyme II (ACE2) receptor, brings conformational changes and promotes the fusion of S2 domain with host cell membrane (Sun et al., 2014a). This binding stimulates signalling pathway via phosphorylation of the receptor by casein kinase 2, which leads to activation of AP1 (activator protein-1) and ERK1/2 (extracellular signal-regulated kinase), CCL2 (chemokine (C-C motif) ligand 2) expression and eventually resulting in pulmonary fibrosis.

Further, the proteolytic cleavage of S protein is crucial to allow fusion. This is achieved by the cell-surface serine protease, TMPRSS2 (transmembrane protease serine 2) which is essential for priming and entry of SARS-CoV-2. The endosomal cathepsins B and L (cat B and catL) facilitate this entry process.

TMPRSS2 is expressed in the human respiratory tract and therefore robustly contributes to both SARS- CoV2 spread and pathogenesis. Particularly, as SARS- CoV-2 entry relies mainly on TMPRSS2, its inhibition is considered as a powerful therapeutic approach. Subsequently, through clathrin-dependent or clathrin-independent ways SARS-CoV-2 enters the host cell via endocytosis (Algarroba et al., 2020). The host cell lysosomal enzymes such as catL and trypsin facilitate the release of viral genome into the host cell cytosol.

Viral RNA synthesis and translation:

After release, the virus alters the host transcription process to its favour through the onset of complex events of viral gene expression. Consequently, ribosomes translate the viral RNA via a cap-dependent mechanism to produce pp1a and pp1ab (two large polyproteins) which are further processed to produce 16 non-structural proteins (nsps).

The RTC assembly on the modified ER membrane is associated with viral RNA synthesis. The establishment of the viral RTC is vital for virus replication and therefore a promising target for antiviral agents against SARS- CoV-2. The RTC is produced in DMVs synthesize a cluster, including subgenomic RNAs in a discontinuous transcription manner.

Using (-) strand intermediate RNA, a series of genomic and subgenomic RNAs are produced. The new genomic RNA molecules are encapsidated with structural proteins M, N, S and accessory proteins and incorporated into progeny virions on membranes of the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). Ultimately, the viral particle loaded vesicles are attached with the plasma membrane to release the virus.

4.5 Variants of Coronavirus:

Genetic variants of SARS-CoV-2 have been emerging as a result constant mutation and they are of serious concern globally. WHO classifies SARS-CoV-2 variants as Variants of Concern (VOC) and Variants of Interest (VOI). Besides, Variants of High Consequence (VOHC) are also included. A variant has one or more mutations that distinguish it from other SARS-CoV-2 strains. The documented variants so far are: α, β, γ, δ and δ^{+}.

4.6 Conclusion Remarks:

High transmissibility and pathogenicity of SARS-CoV-2 is due to a high mutation rate leading to the synthesis of different protein structures such as S protein compared with SARS-CoV and MERS-CoV (Wang et al., 2020a). In addition, CoVs may adapt swiftly to varying ecological niches due to high recombination frequencies that originate from the complex mechanisms.

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5. Virology, Epidemiology, Pathophysiology and Prevention of Covid-19

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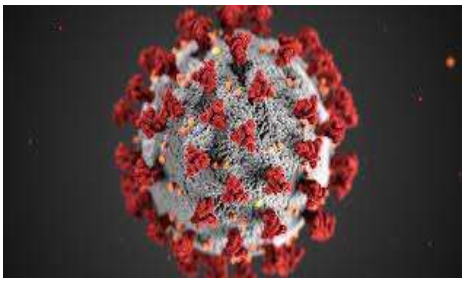
5.1 Topics Covered:

- Introduction to virus and coronavirus
- Virology of covid-19- genome, viral entry, replication of coronavirus into host.
- Epidemiology of covid-19
- Pathophysiology of covid-19- structure of coronavirus, life cycle, host response to coronavirus, symptoms, complications.
- Prevention and control of coronavirus.



Viruses have existed as long has life been on earth. The study of viruses is called VIROLOGY. Experiments on virology began with experiments of Jenner in 1798. He did not know the cause but found out that the individual exposed to cowpox did not suffer from small pox, to test this idea, he inoculated an 8- year old boy with fluid from a cowpox pustule and later intentionally infected the child with small pox. As predicted the child did not develop small pox.

Ref- kuby immunology 6th edition, news medical life science new-medical.net

5.2 Introduction/Classification of Virus:

The coronaviridae family of virus are enveloped, positive sense, single stranded RNA with helical capsids grouped into 4 genera: alpha-coronavirus, beta-coronavirus, gamma and delta-coronavirus that primarily infect birds and mammals, of which alpha and beta coronavirus are known to infect humans. Coronavirus have been studied for decade using the model beta coronavirus, murine hepatitis virus (HIV) and the human alpha coronavirus HCoV-2. Human coronavirus (HCoV-229E, -NL 63, -OC43, -HKU-1) contribute to seasonal cases of the “common cold” and sometimes linked to more severe respiratory

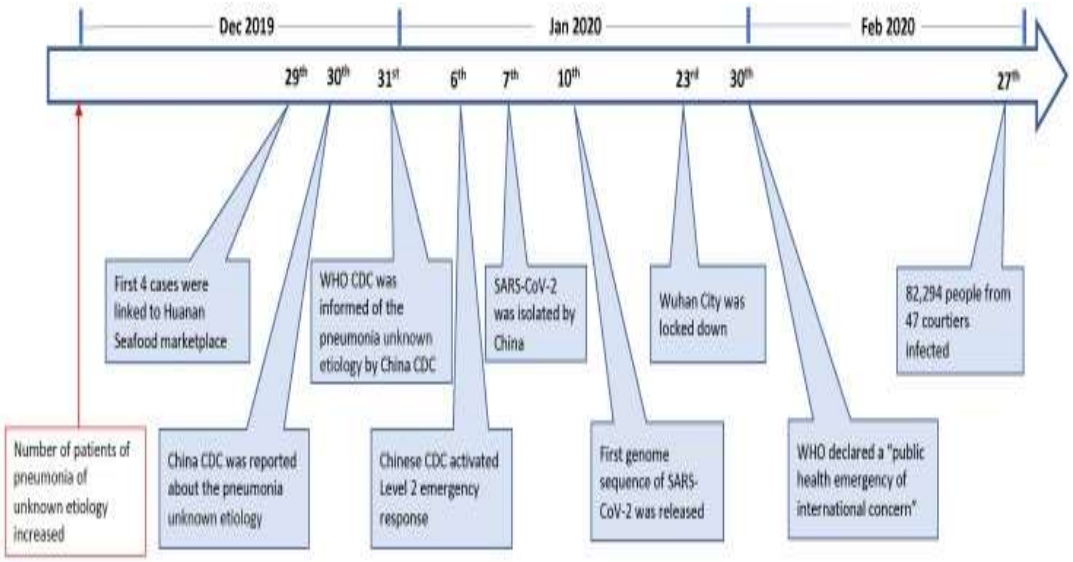
illness. Two beta coronavirus have previously been identified to cause more severe disease and outbreaks, SARS-CoV responsible for the SARS worldwide outbreak in 2002-2003 middle east respiratory syndrome (MERS- CoV) responsible for 2012 MERS outbreak and most recently severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) emerged in 2019.

5.3 Introduction to Coronavirus (SARS-CoV-2):

In December 2019, Wuhan- the Chinese city, new coronavirus SARS- CoV-2 was first identified and expanded across China and beyond. The outbreak of SARS-CoV-2 was considered to have originally started via a zoonotic transmission associated with the seafood market in Wuhan. What started as an epidemic mainly limited to China was declared a pandemic by the World Health Organization (WHO) on March 11, as it has been impacting a large number of people worldwide.

Coronavirus disease 2019 (Covid-19) is defined as illness caused by a novel coronavirus called Severe acute respiratory syndrome coronavirus 2 (SARS), it is known to infect both humans and animals, in humans causing respiratory illness (primarily affect respiratory system) other organ system are involved too. In initial cases symptoms found were fever, dry cough, headache, weakness, vomiting etc. studies have shown that mortalities are higher in elder patients or people who has existing health conditions.

As precautionary measures, a number of countries implemented social distancing and lockdown to mitigate further spread of virus. In early December 2020, nation began the race to secure vaccines as it perhaps the best hope for ending the pandemic, several drugs including remdesivir, hydrochloroquine and azithromycin etc have been tested in clinical trials yet none proves to be a definite therapy by now.



Ref: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7098030/

Currently two homegrown vaccines for the coronavirus- Covishield and Covaxin, also Russia's Sputnik V has been approved for use.

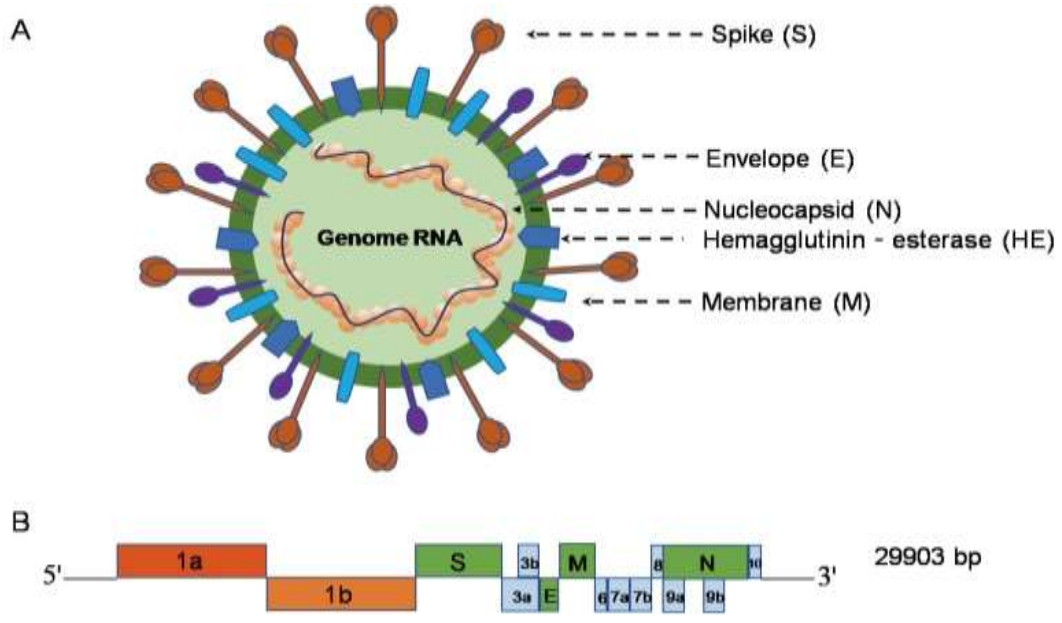
Now we will consider the underlying mechanism to explain the viruses epidemiology, virology, pathophysiology through our current knowledge of Covid-19.

5.3.1 Virology of Covid.

a. **Genome:** Covid-19 belongs to genera beta-coronavirus, it has the largest genome of all ribonucleic acid (RNA) virus infecting humans, it consist of a positive sense single stranded RNA roughly 300kb in size that is 5'-capped and 3'-polyadenylated, associated with a nucleoprotein within a capsid comprised of matrix proteins. This envelope bears club-shaped glycoprotein projections, which plays a essential role in binding to receptors on the host cell, spike protein of coronavirus is functionally divided into the S1 domain, responsible for receptor binding and S2 domain responsible for cell membrane fusion.

Spike (S) glycoprotein is responsible for the characteristic feature of the coronavirus because it forms crown-like structure on the outer surface of the virus.

Other major structural proteins are- HE (hemagglutinin-esterase) in some beta-coronavirus, membrane (M) and envelope (E) all located on membrane envelope and nucleocapsid (N) protein found in core. This covid-19 (SARS-CoV-2) has genetic polymorphism in the S protein which distinguish it from SARS and MERS-CoV.



Ref: curriculum.covidstudentresponse.org

Image ref: ncbi.nIm.nih.gov

b. **Viral Entry:** In general the life cycle of virus within the host consist of 5 following steps:

- Attachment: virus binding to receptor
- Penetration: enter host cell through endocytosis/membrane fusion.
- Biosynthesis: making of new viral proteins/particles.
- Maturation
- release

specific proteins which cell carry on their surface that allow the virus to infect human cell, is called Angiotensin-converting enzyme(ACE-2), it is present in every organism but the quantity can vary among individuals and in different tissues, cells throughout body. ACE2 expression found high in lungs, heart, ileum, kidney and bladder.

A viral genomic RNA, along with the nucleocapsid, enters the host cell cytoplasm through either receptor-mediated endocytosis or directly through the host cell membrane after binding and fusion of 'S' protein.

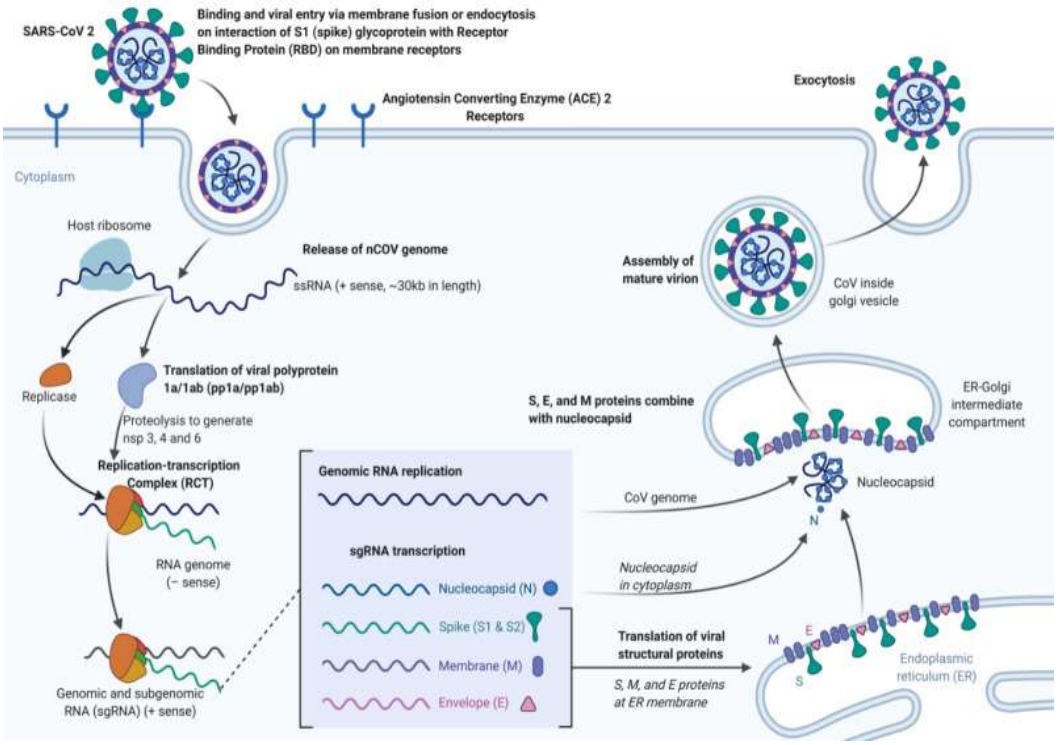
Following binding of SARS-CoV-2 to the host protein, the spike protein undergoes protease cleavage. A two-step sequential protease cleavage to activate spike protein of SARS-CoV-2 consisting of cleavage at the S1/S2 cleavage site for priming and a cleavage for activation at the S'2 site, a position adjacent to a fusion peptide within the S2 subunit.

After the cleavage at S1/S2 site, S1 and S2 subunits remain non-covalently bound and the distal S1 subunit contributes to the stabilization of the membrane-anchored S2 subunit at the prefusion state. Subsequent cleavage at S'2 site presumably activates the spike for membrane fusion via irreversible, conformational changes.

The coronavirus spike is unusual among viruses because a range of different protease can cleave and activate it. The characteristics unique to SARS-CoV-2 among coronaviruses is the existence of furin cleavage site ("RPPA" sequence) at the S1/S2 site.

The furin cleavage sites facilitate a very strong binding of the S-glycoprotein with the hACE-2 receptor of SARS-CoV-2.

c. Replication of Coronavirus in Host Cell:



Covid 19, Corona Replication. Contributed by Rohan Bir Singh, MD

Ref: https://www.ncbi.nlm.nih.gov/books/NBK554776/figure/article-52171.image.f1/

Replication of the virus in host cell. SARS-CoV-2 enters into the host cell by binding with specific cell surface receptors like a human angiotensin-converting enzyme (hACE). S1 and S2 subunit of spike glycoproteins facilitate the process of entry and fusion between the host and the viral cell membrane.

Followed by uncoating, Viral genomic mRNA is entered into the host cell cytoplasm. Two-third portion of the genomic RNA contains two ORFs mainly ORF1a and ORF1b which gets translated into two polypeptides namely pp1a and pp1ab which further gives rise to 16 no of NSPs through the proteolysis process. All these NSP proteins are involving in the replication and transcription process. One-third of the remaining viral genome transcribed into antisense RNA (3′ to 5′), further, it will replicate and formed to a full-length positive strand of genomic RNA with the help of replicase activity of viral RNA dependent RNA polymerase. On the other hand, antisense RNA is also able to synthesize several different small sizes nested (subgenomic) mRNA via discontinuous transcription and further translated into structural proteins like envelope protein (E), membrane protein (M), nucleocapsid (N) and spike proteins (S). Theses structural proteins are assembled into the nucleocapsid and viral envelope at the ER or ERGIC, followed by release of virus by exocytosis or by fusing with the plasma membrane.

5.3.2 Epidemiology of Covid-19:

Epidemiology is the study of the determinants, occurrence, and distribution of health and disease in a defined population.

A large number of studies so far are reports based on experiences in China. Initial reports showed that , its origin was Bat. It transmitted human to human by droplets and contact routes. At the beginning of the outbreak, COVID-19 cases were mostly observed among elderly people . as the outbreak continued, the number of cases among people aged 65 years and older increased further, but also some increase among children (<18 years) was observed.

Following the outbreak in China, SARS-CoV-2 has spread worldwide. As of early April 2020, the reported number of covid-19 patients were highest in the U.S followed by Spain, Italy, Germany, France and China. Italy was significantly affected after the outbreak of China. The report from Italy showed the case-fatality rate of 7.2% which was three times as high as the one in China. The high case-fatality in Italy was somewhat explained by the demographic chracterstics.

The first two cases of the new coronavirus (COVID-19) in Italy were recorded between the end of January and the beginning of February 2020. Since then, the number of cases in Italy increased steadily, surpassing 4.3 million as of August 5, 2021.

(https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.statista.com%2Fchart%2F21346%2Fcoronavirus-in-italy-update%2F&psig=AOvVaw0YNfyEq9U1ZyrWmKL1KfHf&ust=1628420404620000&source=images&cd=vfe&ved=0CAgQjRxqFwoTCOiHkfHgnvICFQAAAAAdAAAAABAD)

Ref: https://www.statista.com/statistics/1101690/coronavirus-new-cases-development-italy/

www.elsevier.com/locate/yclim

A systematic review and meta-analysis was conducted to provide an overview of the epidemiological chracteristics of COVID-19. Findings suggested that COVID-19 has an average incubation period of 5.68 days and there is a lag of 4..92 days from onset of symptoms to the first clinical visit. On average, symptoms of the patients lasts less than 20 days before recovery is achieved. Fever, dry cough, shortness of breath and fatigue are common symptoms among the patients in the included studies. The longer incubation period of the COVID-19 may be one of the major factors that helps explain its rapid spread in comparison with previous respiratory infection viruses.

Ref: ncbi.nIm.nih.gov

from the beginning of this outbreak, the percentage of children within the total COVID-19 patients was small. According to the data of the Chinese Center for Disease Control and

Prevention (China CDC) from February 2020, children younger than 10 years of age and within the age of 11-19 years occupied 1% each of the total cases. Considering this age group represents 20% of the total population, however, this may be underestimation of actual incidence in pediatric population if less tests were undertaken in children due to less symptoms. In the report of 2134 pediatric patients with COVID-19 from the China CDC, 4.4%, 50.9%, 38.8% and 5.9% of patients were diagnosed as asymptomatic, mild, moderate or severe respectively.

(asymptomatic: covid test is positive, without any clinical symptoms and signs.

Moderate: frequent fever, cough with no obvious hypoxemia.

Severe: pneumonia with hypoxemia(Spo2<92%)

Critical: Acute Respiratory Distress Syndrome (ARDS) may have shock, encephalopathy, myocardial injury, heart failure etc.)

In contrast, 18.5% of adult patients had severe diseases. Infants were most vulnerable to severe type of infections; the proportion of severe and critical cases was 10.6%, 7.3%, 4.2%, 4.1% and 3.0% for the age group of 1, 1-5, 6-10, 11-15 and > 16 years respectively.

Overall, the data suggested that children were less asymptomatic than adults as in Chinese reports. Among the children for whom complete information was available, only 73% developed fever, cough or shortness of breath. That's compared to 93% of adults reported in the same time frame, between the ages of 18 and 64 years. Regarding the severity of COVID-19, there is a growing interest in relationship between the severity of disease and gender. Although the Chinese series showed equal number of cases between males and females, data suggested that more men than women suffered from severe disease and died. The data from other countries demonstrated similar results. Adverse outcomes of COVID-19 were associated with comorbidities, including hypertension, cardiovascular disease and lung disease. These conditions are more prevalent in male and linked to smoking and drinking alcohol. Sex based immunological differences were pointed out as another potential explanation. Within the context of pandemics, found that women were about 50% more likely to practice non-pharmaceutical behaviors, such as hand washing, face mask use and avoiding crowds as compared to men, which may be in part responsible.

Ref: science direct, www.elsevier.com/locate/yclim

5.4 Pathophysiology of Corona Virus:

The convergence of pathology with physiology or the study of the disordered physiological processes that cause result from or are otherwise, associated with a disease or injury is termed pathophysiology. A lot has been discovered about the novel Corona Virus, about how it spreads, its transmission and how fatal it can be but very less is known about the pathophysiology of this virus. In the pathophysiology we will discuss about the Life Cycle of the virus, how it invades the host cell and its transmission.

Corona Virus also known as Covid – 19 or SARS Cov-2 is believed to emerge from Wuhan, Hubei Province, China. The novel Corona Virus belongs to the family Coronaviridae. It affects the human by causing mild fever to major respiratory tract infection and may even lead to death.

The novel Corona Virus was earlier named 2019-n CoV and later named SARS- CoV- 2 (Severe Acute Respiratory Syndrome Corona Virus 2 and now it is termed as COVID – 19 i.e. Corona Virus Disease -2019 (as referred by WHO). The disease caused by this virus has spread like a fire across the world and has been termed fatal by WHO on March11, 2020.

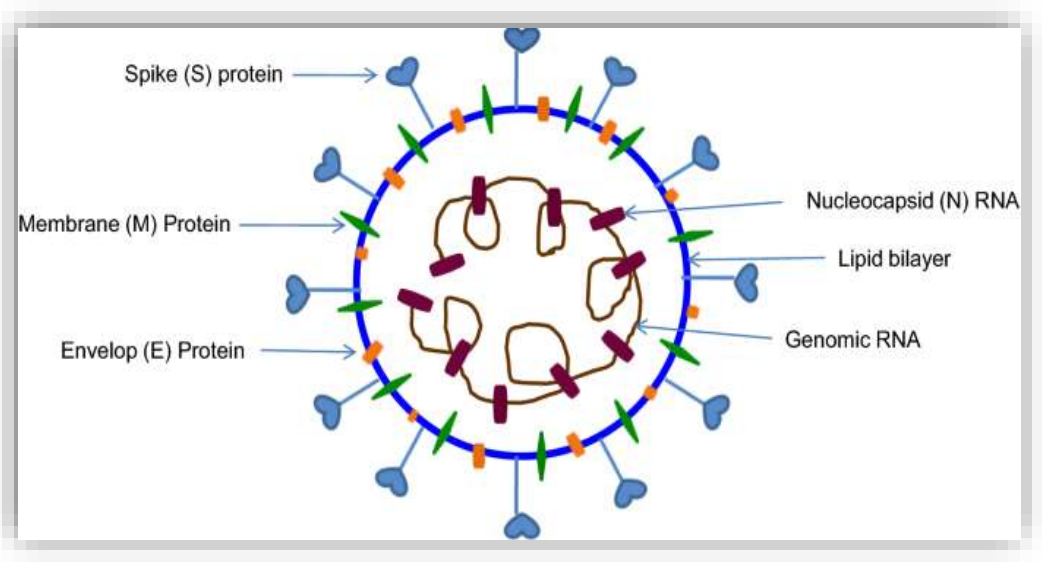


Fig. Structure of corona virus (https://link.springer.com/article/10.1007/s12291-020-00919-0)

- **Transmission of Infection:**

The principal mode by which people are infected with SARS-CoV-2 is through exposure to respiratory fluids carrying infectious virus.

1. Inhalation of very fine respiratory droplets and aerosol particl
2. Deposition of respiratory droplets and particles on exposed mucous membrane in the mouth, nose, or eye by direct splashes and sprays,
3. Touching mucous membranes with hands that have been soiled either directly by virus-containing respiratory fluids or indirectly by touching surfaces with virus on them.

The presence of the virus has been confirmed in sputum, pharyngeal swabs and faeces . Vertical transmission of SARS-CoV-2 has been reported and confirmed by positive nasopharyngeal swab for COVID-19.

5.5 Structure of Corona Virus:

Animal and plant viruses generally fall into two basic categories. Those in which genetic material is long DNA molecule and those in which genetic material is stranded RNA.

Adenoviruses, wart viruses, Herpes fall under the first category and Corona Virus, HIV, rhinovirus, influenza viruses fall under the second category.

The particles of the novel Corona Virus consist of long RNA polymers that are tightly packed into the center of the particle and are surrounded by coats or capsid proteins that consist of repeated protein molecules. In case of the novel Corona Virus the proteins are referred to as nucleocapsid designated by N.

The nucleocapsid proteins form the capsid outside the genome and the genome is packed by an envelope that is associated to link with three structural proteins namely – Membrane proteins designated by M, spike proteins designated by S and envelope proteins designate by E.

SARS-CoV-2 contains four structural proteins and sixteen non structural proteins. SARS-CoV2 particles are spherical and contain proteins known as spikes that protrude from the surface. These spikes latch into the human cells causing viral membrane to fuse with the cell membrane. The viral genes then undergo replication and produce more viruses.

- **Host Response to Corona Virus:**

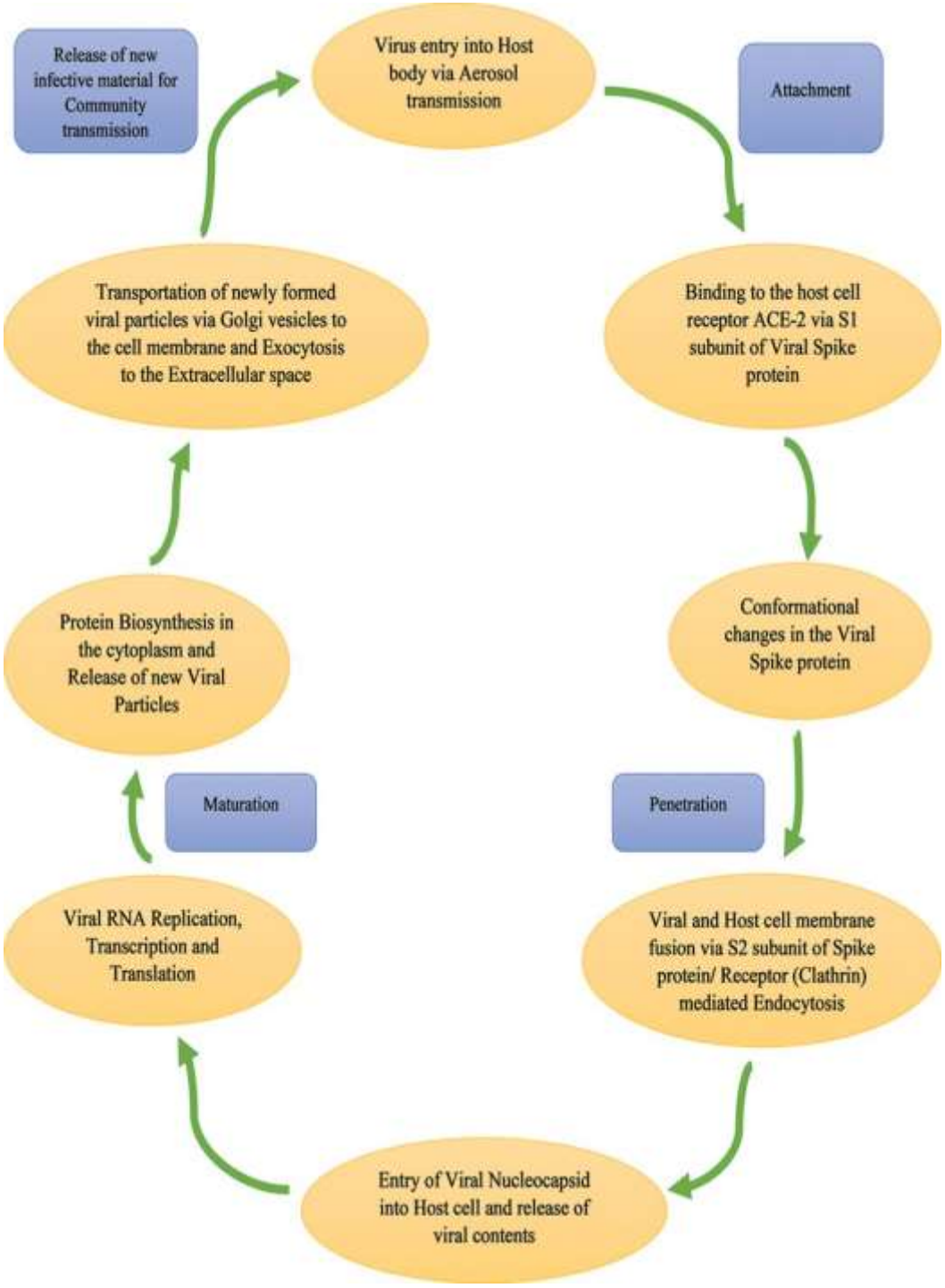
The symptoms of patients infected with Corona Virus ranges from minimal symptoms to severe respiratory failure with multiple organ failure or may even lead to the lead of an individual. Mostly the elderly and the ones suffering from diseases like diabetes are more prone of getting the Virus.

As we all know that Corona Virus transmits the respiratory droplet that comes as a result from coughing or sneezing. It enters our nasal system by inhaling and then the viral genes starts to replicate and hence multiply and cause severe effects on the individual's body.

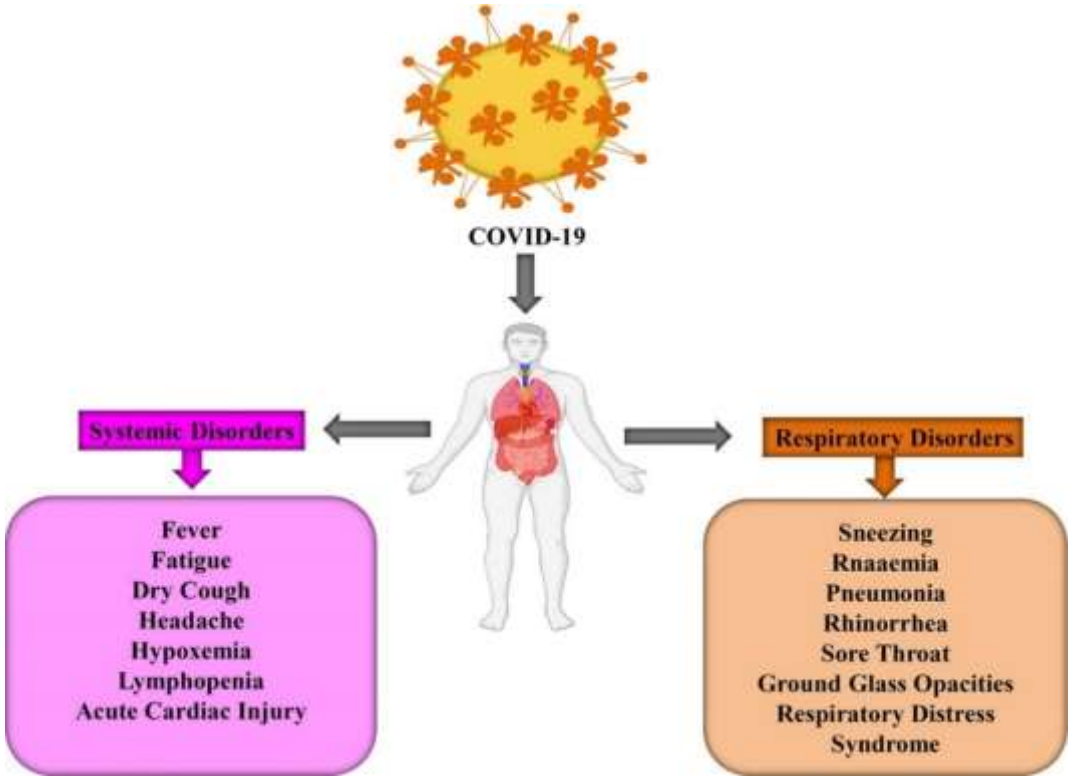
The main receptor for the novel Corona Virus is the ACE2. The enzyme Furin plays an important role for allowing the viral genes to enter the host body.

The spike protein of the Corona Virus is pinched inside the host cell binding to the ACE2. The virus starts replicating and multiplying in number. It then reaches the respiratory tract where it faces more innate immunity response.

The disease is mild for almost 80% of the infected individuals and mostly affects the upper airways and hence, these individuals can be monitored and hence treated. The rest 20% infected individuals suffer from pulmonary infiltrates and may develop severe disease, many of which can be fatal.



https://www.frontiersin.org/articles/10.3389/fphar.2020.563478/full



A. Symptoms:

Signs and symptoms may appear after 2 to 14 days of exposure. Most common symptoms include Fever, Cold, Cough, and Tiredness. Early symptoms may also include loss of taste and smell. Other symptoms include soar throat, chest pain, chills, body aches, headache, difficulty in breathing, nausea, vomiting, diarrhoea, rashes and so on. The symptoms start becoming worse as the virus starts multiplying.

Symptoms vary from person to person and in some cases there might be no symptoms at all whereas others might have severe symptoms. Elderly people have higher chances of suffering from COVID-19. There are certain health conditions that increase the chances of getting diseases or getting affected from corona virus. Some these conditions include pregnancy, heart diseases, diabetes, obesity, high blood pressure, smoking, chronic kidney disease, brain and nervous system conditions, dementia and many other serious conditions.

B. Asymptomatic Phase:

The SARS-CoV-2 which is received via respiratory aerosols binds to the nasal epithelial cells in the upper respiratory tract. The main host receptor for viral entry into cells is the ACE-2, which is seen to be highly expressed in adult nasal epithelial cells.

The virus undergoes local replication and propagation, along with the infection of ciliated cells in the conducting airways. This stage lasts a couple of days and the immune response generated during this phase is a limited one. In spite of having a low viral load at this time, the individuals are highly infectious, and the virus can be detected via nasal swab testing.

Invasion and Infection of The Upper Respiratory Tract:

In this stage, there is migration of the virus from the nasal epithelium to the upper respiratory tract via the conducting airways. Due to the involvement of the upper airways, the disease manifests with symptoms of fever, malaise and dry cough. There is a greater immune response during this phase involving the release of C-X-C motif chemokine ligand 10 (CXCL-10) and interferons (IFN-β and IFN-λ) from the virus-infected cells. The majority of patients do not progress beyond this phase as the mounted immune response is sufficient to contain the spread of infection.

Involvement of the Lower Respiratory Tract and Progression to Acute Respiratory Distress Syndrome (ARDS):

About one-fifth of all infected patients progress to this stage of disease and develop severe symptoms. The virus invades and enters the type 2 alveolar epithelial cells via the host receptor ACE-2 and starts to undergo replication to produce more viral Nucleocapsids. The virus-laden pneumocytes now release many different cytokines and inflammatory markers such as interleukins (IL-1, IL-6, IL-8, IL-120 and IL-12), tumour necrosis factor-α (TNF-α), IFN-λ and IFN-β, CXCL-10, monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1α (MIP-1α). This 'cytokine storm' acts as a chemoattractant for neutrophils, CD4 helper T cells and CD8 cytotoxic T cells, which then begin to get sequestered in the lung tissue. These cells are responsible for fighting off the virus, but in doing so are responsible for the subsequent inflammation and lung injury. The host cell undergoes apoptosis with the release of new viral particles, which then infect the adjacent type 2 alveolar epithelial cells in the same manner. Due to the persistent injury caused by the sequestered inflammatory cells and viral replication leading to loss of both type 1 and type 2 pneumocytes, there is diffuse alveolar damage eventually culminating in an acute respiratory distress syndrome.

Ref: https://pmj.bmj.com/content/97/1147/312

5.6 Complications:

There are many complications that one can suffer due to corona virus. These complications include blood clotting, difficulty in breathing, pneumonia, fatigue and tiredness, organ failures, heart problems, acute respiratory distress syndrome, kidney injury or even failure, dizziness, anxiety, problem in sleeping

5.7 Reference:

1. https://www.biophysics.org/blog/coronavirus-structure-vaccine-and-therapy-development

2. https://www.mayoclinic.org/diseases-conditions/coronavirus/symptoms-causes/syc-20479963#:~:text=Coronavirus%20is%20a%20family%20of,East%20respiratory%20syndrome%20(MERS)
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7169933/
4. https://www.frontiersin.org/articles/10.3389/fcimb.2020.587269/full

5.8 Prevention of Covid-19:

Before understanding the prevention of covid -19 let us first understand how it spreads.

This highly pandemic Corona Virus spreads through close contact (within 6 feet) during person to person contact through respiratory droplets. According to Dr David Goldberg, Corona Virus spreads through respiratory droplets produced when a person sneezes, coughs or when a person comes in direct contact with an infected person like while shaking hands.

Corona virus can also spread by Airborne transmission. There are less chances of transmission by this process.

It can spread when infected air particles linger in the form of air particles or droplets and remain there for few minutes to few hours.

It can spread when the transmissions occurred within enclosed places with less ventilation. In such places, the virus can spread from person who is already infected whether he or she is even at a distance of 6 feet or it can spread from person who was infected with the virus but would have recently left the place.

The corona virus can spread through contaminated surfaces or areas. The chances by spreading of Corona Virus through this means is very less. In this case when a person touches the contaminated surface or any article or thing that has virus on it and later on touches their nose, hands, eyes, mouth, etc. or even come in contact with other people through handshake, it can spread. However, the chances of spread through this means is very less.

- **Prevention of Corona Virus:**

There are various means by which we can control the spread of Corona Virus and hence, lead to its end. Various measures can be adopted like social distancing, washing hands properly, wearing mask, restricting travel, watching for symptoms, treatment of infected person, education and creating awareness.

Prevention and Control of Corona Virus can be done at three levels:

- National Level
- Case- related population level
- General population level

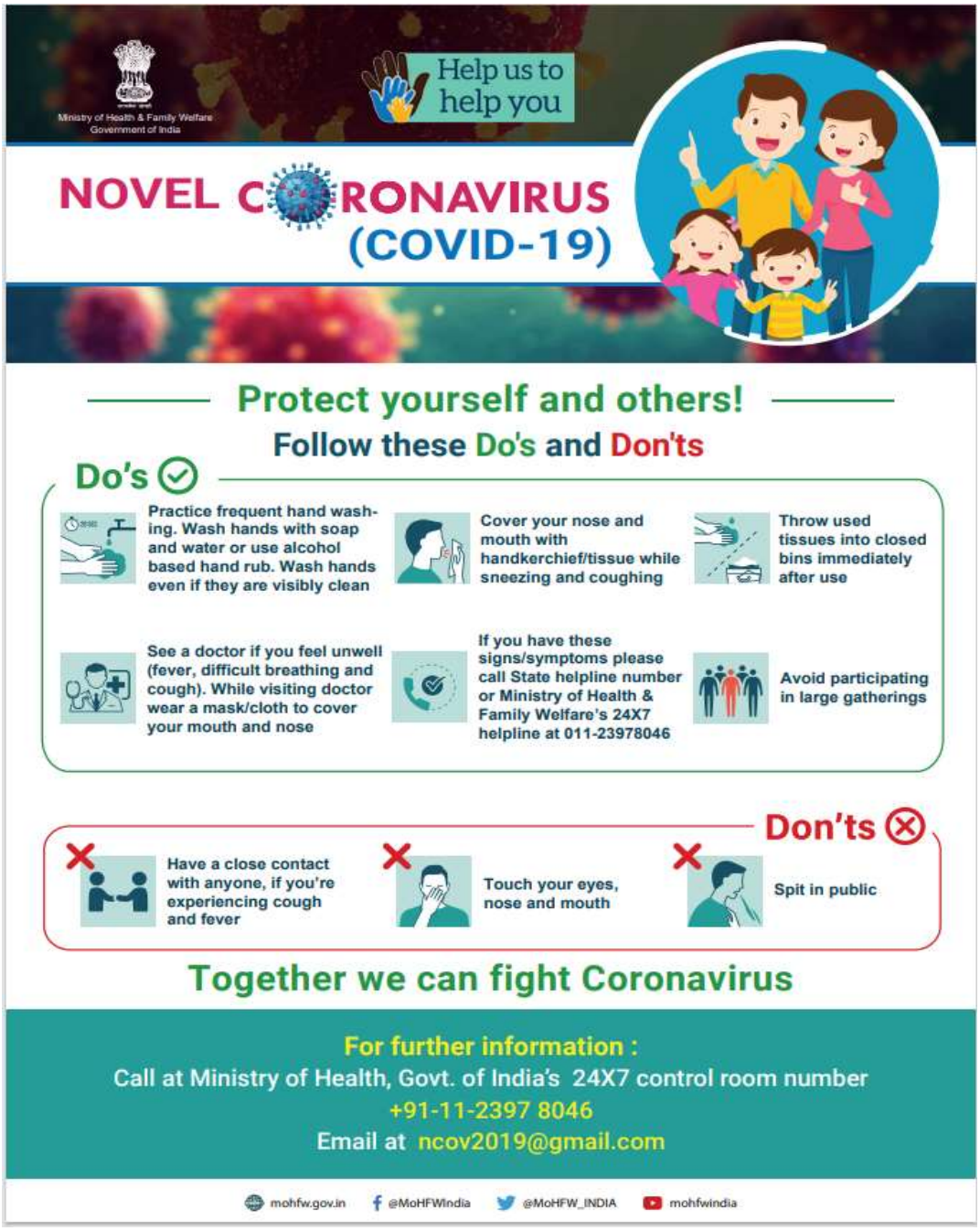


Illustration (1) Poster regarding hand washing, prepared by Indian Ministry of Health https://www.mohfw.gov.in/pdf/Poster_Corona_ad_Eng.pdf

Steps Taken by The Government of India to Stop the Spread of Corona Virus:

1. The Government introduced an app named AarogyaSetu so as to educate the citizens about the deadly Corona Virus and help to create awareness among the people so that they can take preventive measures accordingly.
2. The Oil ministry spokesperson told that the poor households that use 5kg cooking gas cylinders will be provided for free eight refills in three months during the lockdown.
3. The Government set up chains of shops named 'SURAKSHA STORES' which will help the citizens to get daily essentials while maintaining the strict safety rules.
4. Ramesh Pokhriyal (Union Human Resource Development Minister) launched a web portal named YUKTI to monitor and record the initiative by the ministry.
5. The Government provided free LPG refills to over 8.3 crore poor women for 3v months during the lockdown.
6. The government doubled the collateral free loan amount for women in self help groups.
7. Over 6 crore farmers have been benefitted during the lockdown under the PM KISSAN Scheme.
8. For the workers the wages were hiked from Rs. 182 to Rs. 202 under the MGNREGA.
9. The last date for filling the income tax returns for the financial year 2018 to 2019 was also extended to June 30, 2020.
10. Under the Building and Construction Workers Fund over 2 crore construction workers received almost Rs 3,066 crore as financial support.
11. Even the deadline for filling the GST was extended to JUNE 30,2020.
12. The government provided medical insurance cover of almost Rs. 50 lakh per person to health workers fighting during the corona virus pandemic

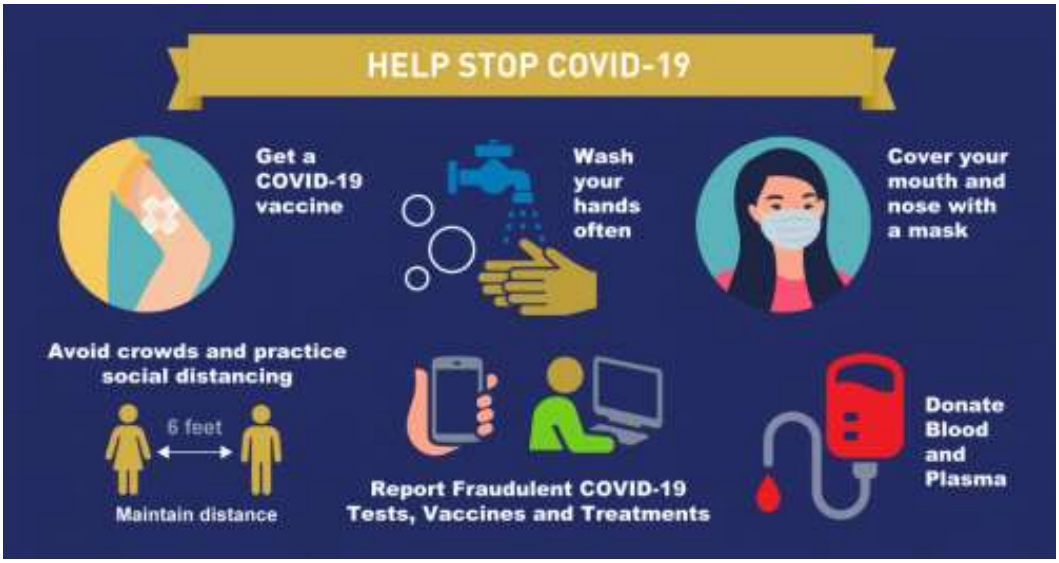
This is not the end. The government did all that it could. It helped the society in a number of unexplainable ways. Some of which got published and other did not.

Measures To Control Corona Virus:

- Wash hands most often. One can use soap and water or an alcohol- based hand rub.
- Wear a mask whenever outside.
- Maintain physical distance from someone who is sneezing or coughing.
- Don't touch your eyes, nose or mouth.
- Cover your nose and mouth with bent elbow or carry an handkerchief or a tissue.
- Stay home whenever you feel unwell.
- If you have fever,cough or sneezing take immediate medical help.
- Use hand sanitizer after touching the surfaces or even after shaking hands.
- Refrain from smoking and other activities that makes your lungs weak.
- Avoid large gatherings.
- Get vaccinated as soon as you are eligible.
- Wash fruits and vegetables properly before consuming.
- Low carb diet will help slow down diabetes and focus on protein rich diet.
- Fruits and vegetables rich in beta carotene, ascorbic acid and other essential vitamins should be consumed.
- Some natural immunity boosters like turmeric, ginger,gooseberries (amla) can be taken.
- Herbs like Garlic, basil leaves and black cumin also increase immunity.

- Certains nuts and seeds like sunflowers seeds, flax seeds,pumpkin seeds and melon seeds, etc. are rich in proteins.
- Take proper sleep.
- Stay hydrated.
- Do not skip exercise.
- Consume supplements or food that boosts immunity like vitamin C, Vitamin D, Zinc, Elderberry,Turmeric and Garlic.

Reference (https://www.redcross.org/about-us/news-and-events/news/2020/coronavirus-safety-and-readiness-tips-for-you.html)



Ref (https://www.fda.gov/consumers/consumer-updates/help-stop-spread-coronavirus-and-protect-your-family)

5.9 Cleaning and Disinfection:

High-touch areas such as bedside tables and door handles should be disinfected daily with regular household disinfectant containing a diluted bleach solution (that is, 1-part bleach to 99 parts water). For surfaces that cannot be cleaned with bleach, 70% ethanol can be used. Toilets and bathrooms should be cleaned and disinfected with a diluted bleach solution (one part bleach to 9 parts water to make a 0.5% sodium hypochlorite solution). Disposable gloves should be used when cleaning or handling surfaces, clothing, or linen soiled with body fluids. All used disposable contaminated items should be placed in a lined container before disposing of them with other household waste. Clothes, bed linens, and bath and hand towels should be cleaned using regular laundry soap and water or machine washed at 60–90°C with common laundry detergent. Disposable gloves should be used when cleaning or handling surfaces, clothing, or linen soiled with body fluids. All used disposable contaminated items should be placed in a lined container before disposing of them with other household waste.

Useful website: https://www.ncbi.nlm.nih.gov/books/NBK554776/

ISBN: 978-93-90847-59-4

6. Clinical Synopsis of Covid 19- An Overview

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6.1 Introduction:

As the SARS-CoV-2 pandemic spread internationally in early 2020 with substantial health and economic effects, so did the disease itself. The coronavirus illness 2019 (COVID-19) has an exponential surge in scientific publications linked to the disease's natural history and the development of diagnostic and treatment techniques. Concerns have been expressed about the scientific quality of the literature despite the need to quickly transmit information to the medical community, government organisations, and the general public. Any of the following four stages of research might lead to a study that is poorly conducted: (1) the selection of a research question relevant to patient care, (2) the quality of the research design, (3) the suitability of publication, and (4) the quality of the research reports. As a result, evidence-based medicine relies on a hierarchy of evidence, which ranges from the highest level of randomised controlled trials (RCTs) to the lowest level of clinical case studies and case reports. This evaluation was conducted because of the consequences for clinical care and policy decision making, as well as concerns about methodological and peer-review standards for COVID-19 research (5). Specifically, we conducted a systematic review to identify COVID-19 clinical literature and matched it to historical controls to evaluate the following: (1) the methodological quality of COVID-19 studies using established quality tools and checklists, (2) the methodological quality of COVID-19 studies stratified by median time to acceptance, geographical regions, and journal impact factor, and (3) a comparison of COVID-19 methodological quality to matched controls.

6.2 Background:

a. CoV-2, a new coronavirus that shares many characteristics with SARS-CoV, is responsible with COVID-19, an acute respiratory illness.
b. Both symptomatic and asymptomatic people can transmit the virus through close contact (less than 6 feet) with respiratory droplets from the infected person. Aerosols and contact with fomites may potentially be a means of transmission, but these are not considered to be the most common.
c. SARS-CoV-2 aetiology includes clinically relevant aspects.:

- Viral spike protein binds to ACE2 receptors on cells, allowing infection. Type 2 transmembrane serine protease is required for cell entry in order to cleave the ACE2 receptor and activate the viral spike protein.
- infected epithelial cells of the nose and lungs, together with pneumocytes.
- A hypercoagulable state and a dysregulated inflammatory response are the outcome of viral replication speeding up and the breakdown of the epithelial-endothelial barrier in later stages.

- An imbalance in the renin-angiotensin-aldosterone pathway may potentially contribute to tissue damage caused by an infection. –

d. On March 11, 2020, the World Health Organization proclaimed COVID-19 a global epidemic. As of June 14, 2021, there have been over 252 million cases worldwide, including over 5 million deaths.
e. COVID-19-related mortality is highly variable and influenced by the patient's age, severity of illness, and other medical conditions. The death toll is estimated at

- Overall, 0.3% to 2.3%, are affected.
- 10% - 23% for patients in the hospital.
- 26% to 50% of patients admitted to the ICU.
- 38% to 88% of patients requiring mechanical breathing or extracorporeal membrane oxygenation will require invasive ventilation (ECMO).

6.3 Evaluation:

a. There is a 2-14 day incubation period, with a mean of 5 days, before mild to severe symptoms appear.
b. Symptoms may include:

- Fever; In few Neither a fever nor chills are present.
- shortness of breath, coughing or difficulty breathing
- a headache, muscle or body aches, dizziness, or fatigue are all possibilities.
- Congestion, a runny nose, or a sore throat are all possibilities.
- a new olfactory or olfactory loss.
- nauseousness, vomiting, diarrhoea, stomach discomfort, or anorexia.
- A loss of consciousness.
- rash.

c. In up to 30% of individuals, an asymptomatic infection may arise.
d. Nucleic acid amplification test (NAAT) for SARS-CoV-2

- NAAT is now the most reliable method for confirming a diagnosis (Strong recommendation).
- Even if clinical suspicion of COVID-19 infection is low, NAAT is indicated for those with symptoms who live in the community (Strong recommendation).
- Patients who are asymptomatic but require hospitalisation due to immune-compromise in locations with a high frequency of COVID-19 may be advised to use NAAT.

e. Nucleic acid testing for the SARS-CoV-2 virus can be done on a variety of specimens. Nasopharyngeal swabs, mid-turbinate swabs, and nasal swabs are the most routinely utilised upper respiratory specimens.
f. First 2 weeks after symptoms begin, serologic testing is not indicated for the diagnosis of SARS-CoV-2 infection (Weak recommendation).

6.4 Management:

a. This decision should be taken on an individual basis, taking into account the patient's condition and the resources available.

- There is no need to hospitalise patients with a minor disease (i.e., no viral pneumonia or hypoxia).
- There are some patients who require hospitalisation because of their comorbidities and the potential for clinical advancement.
- Pneumonia, hypoxemia, acute respiratory distress syndrome (ARDS), sepsis and septic shock, cardiomyopathy, arrhythmia, and acute renal injury are all examples of severe symptoms that necessitate hospitalisation and support.

b. For patients who are not in the hospital.

- Instruct patients to look out for signs and symptoms that indicate an urgent need for medical attention (Strong recommendation).
- Antiviral or immunomodulatory medication such as corticosteroids are not suggested.
- The use of monoclonal antibody spike protein inhibitors may be investigated in patients with mild to moderate COVID-19 who have a high risk of clinical progression (Weak recommendation).

c. Treatment guidelines from the National Institutes of Health (NIH).

- For patients in the hospital:
    - Outside of a clinical trial, monoclonal antibody spike protein inhibitors are not indicated.
    - thromboprophylaxis with low-molecular weight heparin (LMWH), unfractionated heparin (UFH), or fondaparinux at prophylactic doses is indicated (Strong recommendation).

- If no requirement for supplement oxygen:
    - Antiviral or immunomodulatory therapy is not necessary in this case.
    - Patients with moderate disease may be eligible for remdesivir if they are at high risk of clinical deterioration.
    - dexamethasone and other corticosteroids are not recommended unless there is a clinical need for them (Strong recommendation).

- When supplemental oxygen is needed but not high flow device, noninvasive ventilation, invasive mechanical ventilation or ECMO, consider the following options in order of preference:

- Remdesivir 200 mg IV for one day, followed by remdesivir 100 mg IV for four days or until discharge, whichever occurs first (Weak recommendation).
- An IV or oral dose of dexamethasone 6 mg per day for up to 10 days or until discharge is recommended (Weak recommendation).
- if remdesivir is unavailable, dexamethasone (Weak recommendation).
- If significant clinical improvement has not occurred by day 5, remdesivir may be extended to a maximum of 10 days.

- Noninvasive ventilation and high-flow devices should be considered in order of preference if oxygen supply is required, but not invasive mechanical ventilation or ECMO.

  - For up to 10 days or until discharge, dexamethasone 6 mg IV or orally may be administered (Strong recommendation).
  - dexamethasone (at the stated dose and duration) plus remdesivir 200 mg IV for 1 day followed by remdesivir 100 mg IV for 4 days or till discharge, whichever occurs first (Weak recommendation).
  - individuals recently discharged from a hospital with increased oxygen demands and systemic inflammation:

    - In some cases, an additional tocilizumab 8 mg/kg real body weight IV or baricitinib 4 mg daily for 14 days or until discharge to dexamethasone (with or without remdesivir) may be explored (Weak recommendation).
    - if tocilizumab and baricitinib are unavailable, sarilumab and tofacitinib may be considered instead (Weak recommendation).

  - Using remdesivir alone is not suggested.

- ECMO or invasive mechanical ventilation:

  - dexamethasone 6 mg IV or orally for up to ten days or till discharge is suggested" (Strong recommendation).
  - dexamethasone and tocilizumab 8 mg/kg actual body weight IV (maximum 800 mg) may be considered for patients within 24 hours of admission to the intensive care unit (Weak recommendation If tocilizumab is neither available or practical to use, sarilumab 400 mg IV infusion over an hour using a preparation for subcutaneous injection may be investigated (Weak recommendation).
  - It is not advised to take remdesivir by itself.

- For all hospitalized patients satisfying requirements for dexamethasone, other corticosteroids such prednisone, methylprednisolone, or hydrocortisone may be given if dexamethasone is unavailable.

- Remdesivir is the only medicine for COVID-19 licenced by the FDA, but professional organisations' advice on its use vary.

- There are a few other treatments approved by the FDA for emergency use, but their efficacy in COVID-19 is unknown.

- Plasma from patients who have recently recovered from an illness.
- Adults with verified or imminent respiratory failure who are admitted to the ICU for treatment with a blood purification system

d. Hypoxemia and acute respiratory distress syndrome (ARDS), septic shock, and coagulopathy may necessitate further treatment.
e. Supportive care and therapeutic management of COVID-19 are discussed in length in the section under "Management of COVID-19".

Common Clinical Signs and Symptoms:

When SARS-CoV-2 causes COVID-19, the lower respiratory tract is affected (see Table 1). 5,12-14 Fever and a cough are the most common symptoms in most cases. Patients with a "dry" or "nonproductive" cough are more likely to have sputum production than those with a more productive cough.

Dyspnea can be reported or observed, and severity of the disease is associated with the presence of this symptom. 15 Some of the other symptoms include exhaustion and myalgias, as well as pharyngitis and congestion. Diarrhea is a possible gastrointestinal symptom in a few persons.

Table 1: Frequency of Reported Symptoms With COVID-19

Symptom	Observed in Patients With COVID-19(%)
Fever	89-99
Cough	60-79
Fatigue	23-70
Sputum Production	23-24
Dyspnea	19-31
Myalgia	15-35
Headache	8-14
Sore throat	14
Chills	12
Congestion	5
Diarrhea	3-10

As a result, the symptoms of COVID-19 may not be easily distinguishable from those of other viruses. Providers must have a high level of clinical suspicion and rely on the most frequent signs of the disease to make a diagnosis given the breadth of community transmission of SARS-CoV-2. Depending on geographical differences in testing ability, clinical diagnosis may become the norm.

Instructions for home quarantined person:

- The quarantine period at home is 14 days after contact with a confirmed case or earlier if a suspect case is negative on laboratory tests..
- As frequently as possible, use soap and water or an alcohol-based hand sanitizer to thoroughly clean your hands. Do not share household things, such as plates and bowls and utensils such as cutlery, towels, and bedding, with other members of your family or household.
- All the time, wear a surgical mask. Every six to eight hours, the mask should be replaced and thrown away. It is not permitted to reuse disposable masks.
- Close contact masks used in home care should be sterilised with sodium hypochlorite and then disposed of either by burning or deep burial.
- It is important to treat the previously used masks as 'possibly infectious'. He/she should go to the nearest medical facility as soon as possible if any symptoms emerge.

6.5 Conclusion:

Coronavirus disease (COVID-19) is a virus-induced sickness. There is a new coronavirus out there, and it's been spreading like wildfire. Close contact between people is regarded to be the primary mode of transmission. Resources on crucial topics including symptoms, hazards, and how to protect yourself and your family can be found on this page.

On our website, we also offer pages on COVID-19 testing and vaccines, including the ones that have been approved in the United States and others that are still in development.

6.7 References:

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