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REVIEW PAPER

SARS-CoV-2; What leads to death and what prevents it?

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ABSTRACT

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2 is a novel coronavirus, causing COVID-19 infection globally and is tested to be of zoonotic type. Being a virus, it enters the human body and hijacks the host cell to reproduce itself, increase in number and spread by direct or indirect contact among the human race, thus causing suffering and death on large scale. SARS-CoV-2 has been spreading very fast worldwide and affecting the human population since day one of infection severely, causing various problems regarding the normal functioning of human body. It's been causing damage to the respiratory system, gastro-intestinal system, cardiovascular system and even the central nervous system. The major drawback of this disease is the imbalanced functioning of immune system resulting either in overpowered viral activity suppressing thehost's anti-viral response or patient's very own immune system being overwhelmed under the condition known as cytokine storm and attacking its own cells, both leading to death.The application of techniques like herd immunity by both direct exposure and vaccination are the solutions with maximum efficacy to cure the disease extensively. Along with that, use of suitable drugs to stabilize the immune system and prevent cytokine storm will be a smart strategy towards controlling the pandemic.

Keywords: - ACE2 receptor, cytokine storm, ARDS, herd immunity, vaccination.

INTRODUCTIO

One of the widespread diseases, gastric ulcer, is supposed to be due to an imbalance between A highly pathogenic and new coronavirus, named as SARS-Cov-2 (severe acute respiratory syndrome coronavirus-2) emerged in the city of Wuhan, China. The disease is termed as COVID-19, coronavirus disease in 2019. [1]This virus has genetic similarity of about 93% with the Bat coronavirus RaTG13. [2] Its first case was detected back on 17 November 2019 but the disease was first identified in December 2019 and since then owing to its transmittable nature, it has caused multiple outbreaks leading to a fast spreading pandemic. This virus is the youngest in the whole family of coronavirus known to infect humans, having already resulted in large number of deaths worldwide.Both the internal and external factors of the disease and the virus are introduced throughout the paper.

This paper talks about the different aspects of this coronavirus which includes the factors responsible for the increasing mortality rate like binding of virus at ACE2 receptor, its hijacking mechanism of the host cell, the post-hijacking scenario inside the host body,direct infection, cytokine storm, effect on various organs resulting in multiple organ failure, ARDS (acute respiratory distress syndrome), systemic inflammatory response, neurological distress and cardiovascular effects. These topics are discussed at par with close relevance and inter-dependence with each other as well as the external

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environment. A complete web of inter-connection between the cells of the host body affected by the viral infection has been knitted in order to explain the entire concept of hijacking of the host cells by the virus and causing disturbances in normal body mechanism with their outcomes as illness and death.

Treatment methods and ideologies against the disease like the concept of herd immunity as direct exposure and through vaccination has been discussed in detail. The diagnostic and treatment idea of cytokine storm has also been thrown some light on which includes the administered use of drugs like alpha blockers or different approaches such as antibody neutralizers, chemokine inhibitors and more. Vaccination has been given a specific focus in relevance with the recent clinical trials and types of approaches used against COVID-19 across the globe. The required understanding of vaccines and vaccination in the case of this disease has been elaborated as well. Works and the candidates for vaccination race to cure COVID-19 are also talked about.

SARS-CoV-2

The novel SARS-CoV-2 is a member of Coronaviridae family in the Nidovirales order. [3]There are prominent crown-like spike proteinspresent on the outer surface of this virus, thus it is named as coronavirus.Virus measures 120nm in diameter and falls under the β group of further classified coronaviruses.It has been revealed by the genomic analysis that this is phylogenetically similar to the SARS-like bat virus, therefore bats as considered to be the possible reservoirs of the respective virus.[2] The viral genome has approximately 3000 nucleotidesand 26,000to 32,000 nucleotide bases. [4,5]At the microscopic level this virus looks like a multi-faceted crystal or a rough spherical in shape.CoVs (coronaviruses) are the single stranded, positive strand RNA viruses which are also the largest known RNA viruses.They have a circular viral membrane composed of a lipid bilayer which possess several trans-membrane proteins. It is advised to wash our hands with soap and alcohol-based sanitizer because it is the very same lipid bilayer which gets primarily destroyed thereby rendering the virus ineffective.The central core of the virus acts as its brain in the form of a single stranded RNA which is bound to few nucleocapsid phosphoproteins.The spike proteins are the most important for the virus to infect humans as it interacts very effectively with the ANGIOTENSEN CONVERTING ENZYME-2 i.e. ACE2 receptor found in the human cells.There exists,Hemagglutinin acetyl-esterase glycoprotein and membrane glycoprotein (M proteins), which collectively helps the spike protein to efficiently interact with the ACE2 receptor.A small envelope glycoprotein also exists embedded in the viral membrane providing stability to the structure of the virus. [6,9,10]The pictorial demonstration of the detailed structure is given in Figure No.1.

The viral spike protein has 2 receptor binding domains (RBDs) facing in opposite direction, one upwards and other downwards, they allow virusto bind to the human cells. The virus targets the angiotensin converting enzyme 2 (ACE2) receptor which has already been bonded with an amino acid transporter and uses its own spike protein up (one facing upwards) to penetrate the human cells.It dissolves its own protein shell and releases its RNA

inside the host cell. The viral RNA takes over the Endoplasmic Reticulum of the host cell to replicate itself and manufacture the protein parts for producing new viral copies. The hijacked cells' Golgi bodies then package viral RNA and proteins into protein packaged cells. This leads to the creation of a new virus which leaves the infected cell via membrane. Coronavirus takes over the host cell and apoptosisis the result when infection overwhelms the whole cell activity therefore leading to death when number of host cells is affected. [4]

Its common symptoms includecommon cold, fever, cough, fatigue, loss of smell and taste and severe acute respiratory syndrome though the incubation period of this virus' infection ranges between 2-11 days with an average result of showing symptoms on the 6th day.As it also stays on different surfaces such as in aerosol, copper, cardboard, plastic and stainless steel for about ranging from 3 hours to 3 days depending on the surface, it's very essential that proper care of sanitizing of the body surfaces is done after coming in contact with these inanimate surfaces in order to prevent the virus entering the bodyas the transmission from people to people has been widely confirmed and till date no clinically approved anti-viral drug or vaccine has been put into use against the disease. [7]

WHAT LEADS TO DEATH?

Direct infection

There are certain common factors which have been noticed in the patients who are easily infected by this virus like people with low body immunity, chronic illness like heart disease or diabetes and post-transplant patients.

As the mechanism stated above, it is clearly depicted that SARS-CoV-2 takes over the human cells' activity and uses it to replicate itself. Therefore, it turns out to be fatal by causing various disturbances in the different organs and resulting into a specific organ or system failure. But there is another reason which increases the fatality rate i.e. the cytokine storm and is considered a major threat to heart and lung failure.

Huge worry about the effect on heart and lungs is because SARS-CoV-2 affects lungs and heart through direct infection. ACE2 receptor ishighlypresent in the lung cells (alveolar cells) which is why lungs are the most affected organs by the COVID-19 infection.But ACE2 receptor is also found in other cells such as heart, kidneys, intestines or testicles.In fact, these receptors seem to be widespread throughout the brain with particular focus where neurons are involved in heart and lung functions, this opens the possibility of opening the covid-19 infecting the brain.Major characteristic of the disease is the respiratory distress and due to this infection, direct infiltration of lungs take place which cause damage to the tissue and may cause cytokine storm.

The events which happen inside the infected cell are given as follows;

a) Once the virus enters the host body through inhaling, mucous or any open wound it reaches the respiratory tract or blood stream and effectively binds to the cells having ACE2 receptor.
b) Following this virus-cell interaction, the viral membrane fuses with the host cell membrane facilitating the viral RNA into the host cell.

This phenomenon makes the individual infected with the virus, itself being asymptomatic.

c) Immediately the host ribosomes confuse viral RNA with the host RNA and start translating the viral RNA.

d) From the 5`region of the positive strand of the viral RNA the translation begins which includes the following; leader sequence, URT (untranslated) region, RNA dependent RNA Replicase, set of three important structural proteins- spike protein(immature), envelope protein and membrane proteins which enables the viral transcript, regulates viral transmission and helps in functioning of eukaryotic ribosomes, replicate viral RNA genome, interacts with ACE2 receptor to penetrate the host cell, viral assembly and release and impart circular shape to the virus respectively.

e) Once translated all these structural proteins are transported to the lumen of Endoplasmic Reticulum where they are glycosylated, here all these proteins attain maturity.

f) Then they are transported to the Golgi bodies through vesicular transport where glycosylation ends.

g) On maturation, these proteins assemble and polymerize to form the nucleocapsid and stays inside the Golgi bodies until they receive the replicated RNA.

h) Ribosome now translates nucleocapsidprotein (only protein inside the core of viral structure) which helps in replicase-transcriptase complex formation. Helps viral RNA packaging and binds viral genome in specific conformation.

i) Ribosomes now glide to the 3` UTR (untranslated) region, UTR of coronaviruses contains a conserved~55 nucleotide pseudo-knot structure which is necessary for viral replication.

j) Lastly before disintegrating, ribosomes glide over the poly A tail which protects the viral RNA from enzymatic degradation in the cytoplasm and aids in translation termination.

k) Now the viral RNA replicates by RNA-dependent RNA polymerase or RNA replicase which creates a complementary stand as negative RNA strand. The negative strand serves as the template for the production of many positive RNA strands for new viral bodies.

l) The positive strands bind to the nucleocapsidafter replication and condenses which is then transported to Golgi bodies and packs into viral particles while the negative strand stays in the cytoplasm of the host cells for producing more copies of viral RNA.

m) Cycle repeats and number of virus increases in the host body and now they are also capable of transmission , therefore its replication will not be only limited to the cells in one host instead the cycle will again begin in another host and continue to others leading to a pandemic which is the very situation of current scenario. [4,8,10]

The pathogenesis of viral attack is shown in Figure No.2.

Cytokine storm

A significant portion of those who are infected with the new coronavirus may not show any symptoms at all and even those who develop symptoms, the majority of those cases are mild but we also know some people who are severely affected from this disease. So why people react

differently to the virus. As this is a novel coronavirus body does not have a specific antibody against it thereforeit is thought that it's the overdrive of the immune response that's leading to the severe cases of COVID-19.Immune system response to the infection is very robust showing symptoms such as shortness of breath. Doctors around the world are trying deciphering the difference between a protective versus a pathologic immune response to this disease.

In normal immune response, the immune response kicks in and it starts to recruit cells from the blood known as white blood cells to clear the virus. But in certain patients we see that immune system actually goes into overdrive. Instead of simply getting rid of the virus, the immune system starts secreting cytokines and instead of helping the host cope with the infection, the cytokines actually cause damage to the tissue, such as breaking down protective lining of the lungs and blood vessels. [12]

The immune response to SARS-CoV-2 infection has 2 phases: -

- Phase 1– Moderate symptoms. The cytokine response used to eliminate the virus causes inflammation.
- Phase 2– Severe symptoms. Hyper inflammation and destructions of lung tissue. Uncontrolled inflammation called 'cytokine storm.' Can result in severe tissue damage, ARDS (acute respiratory distress syndrome) and even death. [13]

Cytokines are soluble molecules which serve as messengers for immune system and they consist of various proteins and glycoproteins. They are produced by wide variety of immune cell types namely, neutrophils, basophils,eosinophils, mast cells, dendritic cells, monocytes, macrophages, B cells and T cells. They are molecules which serve as inner cellular mediators by binding to specific receptors called cytokine receptors on the surface of cells. They change the activity of the cell by altering the function of proteins or by changing the expression of certain genes. They have differing effects like activity of some cells increase and of some cells decrease. [15] Ultimately cytokines have impact on growth, development, maturation, activation and life span of immune cells.Structural groups of cytokines include,

- Interleukins (IL)– 35 known interleukins exist. They are the cytokines which communicate between white blood cells. They are produced by leucocytes to act on leucocytes. They play a key role in immune response and are further classified into, pro-inflammatory (IL-6, IL-6, IL1α, IL1β) and anti-inflammatory (IL-4, IL-10, IL-13) interleukins. IL-6 and IL-10 are one of the key mediators of cytokine storm.[14,15,]
- Tumor necrosis factor (TNF) – They are 9 known types and are produced by mast cells, macrophages and T cells. Play a major role in immune cell activation, differentiation, growth and death. TNFα is the major pro-inflammatory cytokine which is capable of being involved in potent activation of cytotoxic T cells and also plays the central role in viral disease and cytokine storm. [13,14]
- Interferons (IFN) – They are 20 IFNs in humans and they have the ability to interfere with the viral replication. They are further classified into 3 types out of which two are, type 1 (INF-α, INF-β) and type 2 (INF-γ). As their name suggest, they have an 'anti-viral' role. [17]

- Colony stimulating factor (CSF) – These essentially act on the stem cells in bone marrows to stimulate growth and differentiation into specific cells. They are of four types M-CSF, GM-CSF, G-CSF and Erythropoietin.

Lungs, heart, kidneys and brain are adversely affected by the SARS-CoV-2 infection butalong with the direct action of virus on the cells, the uncontrolled and overwhelming immune response generated against invading virus by the host body known as 'cytokine storm' also affectsthem. Cytokine storm syndrome also known as cytokine release syndrome is an over generated response of immune system which is auncontrollable. Inflammation response is first line of defense against pathogens inside the body characterized by redness, heat and swelling and is typically designed to eliminate an invading pathogen but can be dangerous if left unchecked. Inflammation, if not controlled can cause local tissue damage through cytokine storm. Cytokine storm is associated with both infectious and non-infectious diseases and it is also described as an adverse effect of immunotherapy. Cell infection with pathogen leads to immune invasion and then inappropriate immune response is generated which eventually causes cytokine storm therefore severe tissue damage and sepsis occurs resulting to be fatal. [19]

These cytokine storms were historically responsible for many deaths during the 1918 flu pandemic and other viral outbreaks and they are probably behind the most severe cases of COVID-19. Right now, we don't understand and do need to know that what kind of immune response is needed to recover the infection. Elevated cytokine levels are seen in the blood of patients that go on to progressive disease compared to those have recovered. The other thing is that lymphocyte acquires the exhausted phenotype in the patients that go on to progressive disease. And ultimately the lymphocytes become depleted from the patients which is notgood news because a person becomes immune-compromised at this stage.

Patients with severe infection demonstrate lymphocytopenia (severe loss of lymphocytes in blood).The cytokine storm explains the low T cells in patients because high levels of some cytokines such as IL-6, IL-10 and TNFαare inversely co-related with T cells count therefore suppress the T cell activation. Cytokines could be released by the inflammatory macrophages and other innate immune cells. In early stages of the disease, the immune system helps to protect against the virus and reduce the viral load but later on the patient's own immune system may cause lung disease or multi-organ failure and leads to death**.** Applying broad anti-inflammatory may dampen the immune response but could also impair the ability to eliminate the viral pathogen. They may also make the patient more susceptible to secondary infection and could even worsen the outcome. [18,26]

Cytokine storm is nothing but the more immune response than it should be. In an infection, an immune response is necessary to combat the pathogen butin COVID-19 patients this is becoming much deregulated immune response. In normal cases the immune response increases initially and then slowly resolves with the time but in case of cytokine storm the immune response keeps on increasing. This results in release of large number of chemokines, pro-inflammatory cytokines as well as many different types of cytokines. Chemokines

are a separate set of molecules that really help to direct the movement of WBCs in the body. These molecules are pro-inflammatory and helps to bring monocytes, macrophages and other lymphocytes to the site of infection. All these factors are related to the morbidity and mortality we see in the patients.[21]

Virus replicates within local macrophages, causing cytokine release, acute inflammation and increase blood flow so leucocytes can reach the extra-vascular sites of infection. Recruitment of additional immune cells amplifies the cytokineresponse. With inflammation, comes an associated up-regulation of mechanisms to restrain immune responses which preserve local tissue. However, balance and down-regulation of inflammation may not always occur resulting in overabundance of inflammatory cytokines. [19]Progression of cytokine storm most often appears to begin inside the alveoli of lungs of the host body: -

a) In alveoli we have these type2 pneumocytes which are the ones responsible for producing surfactant.
b) When virus gets inside the alveoli, they get attached to these cells via ACE2 receptor. Inside one of the cells viral replication is taking place and virus is making many copies of itself. Eventually the host cell will burst and release the replicated virus.
c) Due to the damage of the cell, cytokines and inflammatory markers will be released.
d) An addition to that, the antigen here is going to come in contact with our antigen presenting cells like dendritic cells. These are the essential part of the body's anti-viral immunity and produce three important things in series; produce IgM and IgG antibodies, stimulate humoral and cellular immunity which is mediated by B and T cells and then B and T cells produce inflammatory cytokines.
e) This is normal but, in some people, it can lead to deadly, uncontrolled, local and systemic inflammatory response. Thus, cytokine storm leads to the powerful attack by the immune system on body.
f) It begins in lungs and spread to the rest of the body. In the lungs what happens is the over production of pro-inflammatory immune cells and cytokines causing edema and inflammation which can cause respiratory distress, ARDS (acute respiratory distress syndrome) and can also lead to secondary bacterial infection.
g) T cells and natural killer cells are potent contributors to cytokines in inflammatory response and these are going to contribute to vasodilation and edema which ultimately increases extra-vascular pressure, decrease tissue perfusion, lead to endothelial dysfunction and compromise the integrity of endothelial cell junctions.
h) Now all this is going to complicate what is normally going inside the lung alveoli. In addition to that we have plasma proteins and cellular debris that is also going to accumulate.
i) These cytokines here are TNF α and IL-6, the primary contributors to cytokine storm. Other cytokines like INF α, IL-1β as well as some of the chemokines are also found in patient's blood.
j) The cytokine storm in lung alveoli can cause acute lung injury (ALI) which then can progress

into ARDS or acute respiratory distress syndromeand it is severe inflammation that damages the local tissue structure.

k) Ultimately healing can occur with fibrosis though leading to a sort of persistent dysfunction. Certainly, there will be long term effects of this even if the person does survive.

l) Cytokine release from blood and alveolar immune cells result in fibrinolysis due to severity of inflammation.

m) The oxygen transfer efficiency of the lungs is decreased because of the fluid filled in the alveoli causing reductionin blood-oxygen concentration.

n) Severe infections are characterized by alveolar and capillary damage, increased collagen, fibrin deposition and increased cell permeability. [20,23]

o) This entire cytokine storm can happen systemically and have an effect on other organ systems in the body leading to systemic clinical presentations i.e. multiple organ failure. In recent cases we have been observing impact on renal system, hepatic system, cardiovascular, gastro-intestinal system and even central nervous system.

Extreme inflammation can lead to the release of large amount of cytokine in the circulation and start affecting secondary organs, even if the viral load decreases. Even the heart is affected by the systemic inflammation andsome patients experiencemyocarditis without any traces of virus in the heart. In severely affected patientsit is observed that heart function decreases and causes death due to;

- The system inflammatory response to the virus.
- The direct infection causing myocarditis.
- Atherosclerotic plaque instability or rupture. [22]

Generally, blood-brain barrier protects the brain from the entry of virus. It acts like a fortified wall with extra selective access to whatever enters the brain. SARS-CoV-2 jumps through this barrier to enter the brain.Virus infecting the brain is only possible if it manages to enter the blood circulation and cross blood-brain barrier or if it covers the crible form plate that lies between the naval cavity and front base of the skull.Increasing cases of covid-19 throughout the world shows the neural manifestation to infect as well, these includes symptoms such as headaches to stroke, muscle damage usually associated with kidney and liver impairment and loss of sense and taste.Bringing back to the ACE2 receptor, once the virus reaches the brain cells, any neuron expressing ACE2 receptor may be targeted.Brain is affected in two ways by the virus which results fatal;

- Direct inflammation of the brain called encephalitis or of spinal cord called transverse myelitis leading to various rapid onsets of acute symptoms like severe headache, fever, forms of epilepsy like convulsions and loss of consciousness.
- Demyelinating i.e. the degeneration of the fatty sheets around the axons.

Severely affected patients of covid-19 are suffering from the neurological distress which even causes hyposmia and hypogeusia due to hindrance in neural responses.Autopsy revealed the brain tissue edema and partial neuronal degeneration in deceased patients. [23,25]

Possible situations going on inside to human host due to cytokine storm and effect on other organs are briefly explained in Figure No.3.

WHAT PREVENTS IT?

Cytokine storm treatment

Understanding cytokine storm, the cytokines involved and the mechanism by which it is induced is critical for designing the therapies. Damage to lungs is the major hurdle in treating the COVID-19 and ARDS is the leading cause of mortality. Cytokine storm can be detected by the elevated levels of ferritin in blood which normally rangesbetween 12-360 (for men) and 10-150 (for women) but patients with severe COVID-19 show levelsup to thousands because of the pro-inflammatory cytokine signaling. There are also certain biomarker assays to diagnose cytokine storm which includes CRP (C reactive point) and D-dimer. Rapid increase levels of both of them in blood increases the risk of cytokine storm and even causes death.

To treat this, we need to balance less effective reduction viral load and immune response limits. Giving early broad-spectrum anti-inflammatory will reduce the cytokine storm but that will suppress the immune response and let virus overpower. This case can be administered by the giving corticosteroid such as methyl prednisolone about 40-120mg to the patients but this suppresses the immune system of the host very much and has other side-effects too. [28]

Targeted cytokine therapies may prove beneficial as they focus on a specific cytokine without causing widespread effect on the immune system. For example, since we know that IL-6 is elevated in patients with lung disease we can use a specific IL-6 inhibitor which may help in fighting the cytokine storm without widespread affecting the immune system. IL-6 inhibitors are currently used in treatment of many autoimmune disease and many studies and clinical trials of working to find the efficacy of the drug in COVID-19. Extreme inflammation can lead to the release of large amount of cytokine in the circulation and start affecting secondary organs, even if the viral load decreases.[5]

Given the complications and delicate balance of cytokines involved on pro and anti-inflammatory responses, targeting and treating cytokine storm has been difficult.Overabundance of cytokines results in lung tissue damage leading to acute lung injury (ALI) which progress into ARDS that can be fatal. Treatment may not be as simple as anti-inflammatory drugbecausegeneral anti-inflammatory treatments have not been effective, in fact some cases have worsened the outcomes or made individual more susceptible to secondary infections. [20] Other immune modulatory treatments have been or are currently being investigated but it is important that these treatments are specific enough to dampen the cytokine storm with or without causing harmful effects to the normal immune system.Current researches in immune modulatory therapies include neutralizing antibodies, chemokine inhibitors and broad anti-inflammatories. Outcomes of these will be reduced damage, increase efficacy of anti-viral and improve treatment window. For example- antibodies that neutralize IL-6 and TNF functions. We fully don’t understand what makes people more susceptible to cytokine storm and the cause of large amount release of cytokines is still unknown.

A common type of prescription drug known as alpha blocker might break the cycle of hyperinflammation before it ramps up. Researchers are interested in this drug because it is capable of interfering with the cell signaling that triggers cytokine storm and theoretically it can stop the cytokine storm even before it stars. As per the Howard Hughes Medical Investigator Bert Vogelstein and his team at John Hopkins University, giving alpha blockers to the bacterial infected mice lessened the cytokine storms leading to decreased deaths in the journal *Nature* of 2018. For the covid-19 trials patients are treated with the alpha blockers called prazosin, for over six days which comes in brand name of Minipress. If the trials result in safe and effective outcome of the drug it may proceed towards the second trials with the people who have caught the disease but are not hospitalized yet. [27]

Herd immunity

Immunity refers to the body's resistance against any pathogenic species or foreign particle that enters the host body. This can be both innate and acquired but both these types of immunities are attained at an individual level. [11] Immunity which is acquired at a mass level i.e. large number of people are immunized against a specific pathogen, that is termed as Herd immunity. This concept only works in the case of contagious diseases. 'Herd' refers to gather of mass people and the immunity that scales from an individual to a mass of people is 'herd immunity'.It is the indirect protection of the susceptible people in the community from those who are infected by the pathogen by creating more of the people who are already immune against the infection. According to which more immune people will come in contact with the infected ones and no effect will happen to the them therefore the susceptible ones will be protected by the immune people who are acting as a barrier between the infected ones and them.[29] Every contagious disease spread among the population by the transmission of pathogen from one patient to another and the average rate of people whom the disease is transmitted from one infected person is termed as the Reproduction factor or R_0. In case of novel coronavirus, SARS-CoV-2 the R_0 is between 2-6 as seen among the affected populationtill now.

In order to protect the population in a way that no more naive people are affected we need to reach the herd immunity threshold i.e. a specific number of people are required to be immune in order to prevent the disease from spreading. Above this level of immunity, the herd immunity will come into effect and will reduce the transmission rate. Mathematically, herd immunity threshold can be calculated with the help of reproduction factor, R_0 by the formula;

Herd immunity threshold= $\frac{R_0-1}{R_0}$

According to which the herd immunity threshold for covid-19 is estimated to between 60-70%, which means this much of the world population must be immune in order to reach the herd immunity threshold. Herd immunity played a very important role in the eradication process of small pox. [30]

A hypothetical SIR (susceptible, infected and recovered) model of COVID-19 patients which demonstrates the complete concept of herd immunity and its outcome are given in Graph No.1 and Figure No.4.

Basically, herd immunity is the nature's own measure of protecting lives i.e. through creating immunity on large scale and comes into force when everything fails. Benefit of it is that as most of the population will become immune, the chance of disease to spread from infected to the naive will even drop by the probability rule. In order to attain herd immunity threshold there are two possible ways;

a) Direct exposure- Expose the population to the direct contact of virus which will develop the immunity among them within the span of weeks and months. During this people with extreme dysregulated immune system, suffering from chronic diseases, post-transplant patients, elderly people and very small kids should be protected as they won't be able to overcome the viral infection and may die. Even if they are exposed and die, this sacrifice will lead to the betterment of complete mankind. Considering if 60-70% of the population is immune against the virus then it will prevent a lot of transmission and protect many people.

If nothing works then automatically herd immunity's concept of direct exposure will take place according to the evolutionary law.It is impractical as per the current situation for any of the country to treat 60-70% of its population against such a fatal virus all at once, none of them even have the infrastructure to support the treatment at this time of emergency.

b) Vaccination- Another concept of herd immunity is, instead of directly exposing the virus to the population,it can be administrated in the form of a protective vaccine which will also boost the immunity in the individuals on a large scale. It is a more practical approach for current scenario but needs time as the development and production of a very effective vaccine against the novel SARS-CoV-2 is not easy and requires many testing phases for the complete experimentation before going for its mass production. The estimated time for the vaccine trials for COVID-19 is about18 months which is quite a lot time for the general population and situation but if successful it will be the first vaccine in the history of vaccines against contagious diseases which developed in the shortest span of time.

In case of SARS-CoV-2 if we wait for reaching the herd immunity threshold naturally, millions will die so the lifesaving shortcut to attain herd immunity is vaccination. This new virus was identified within a day and the sequence was shared a few days later and because of that the testing began across the globe. Scientists worldwide are committing entire labs to creating the vaccine. World's fastest supercomputer has run thousands of simulations and have identified 77 drug compounds that might effectively stop the virus. Test vaccine production time for the coronavirus (2020) took only 65 days, the shortest out of SARS (2002)- 20 months, Ebola (2014)- 7 months and Zika (2016)- 6 months.

Any potential vaccine has a long way ahead, a long and twisting course full of challenges and trials. In US, generally it takes a decade from start to finish. Once the vaccine is proven to be safe it will be allowed for confinement.

In case of COVID-19, immune response ramps up after 2 weeks of infection but that time is enough for the virus to swarm through the body wreaking

havoc. After it deals with the virus, our immune system remembers the antigens sometimes forever other times for a while. We know that our bodies can remember other coronaviruses (HCOV-OC43, HCOV-299E, HCOV-NL63, HCOV-HKU1) for around 1-3 years. So, if this coronavirus is similar and those vaccines are used, if the virus shows up in our bodies again in that time, our immune system can ramp up much faster with overwhelming force, wiping out the virus before it makes us sick or spread to someone else. [32]

Vaccines make us immune by safely showing a virus inside the body that what it looks like by faking the first infection teaching our body to respond so when it does encounter the real virus, body is ready.

For defeating an infectious disease, we require whole world to come together and in theCOVID-19 race the world has come together like never before. Out of over 100 candidates in the race of vaccine production in May, almost half i.e. 44 are in North America, 17 are in China. And they are funded in different ways mostly by private industries. But the main difference between them is their vaccine platform, how they show the body what virus looks like. There are three ways as taken under for production in current vaccine requirement: -

- First generation vaccines- Some vaccinesinjecte the weakened version of the virus into the body. It can't reproduce or do damage but still has that antigen, so our immune system can learn what to watch out for. That's how we vaccinated against polio, measles, mumps and rubella, flu, chicken pox and rotavirus. This is by far our most tried and true method, but it's a slow way to do it because we have to grow the virus for months in other living cells like chicken eggs, a method we have been using since decades. We call these the first-generation vaccines and there are nine in race as of May. [36]
- Second generation vaccines- Other scientists are trying a newer approach, instead of whole coronavirus they are giving the body just an antigen, a piece they think will activate the immune response. Those antigens also need to be grown sometime in yeast cells or attached to another harmless virus. This is how the vaccine for Hepatitis B, whooping cough and meningitis B works. These are second generation vaccines, the most popular kind in COVID-19 race, with 72 candidates. [36]
- Third generation vaccines- Finally, there's a brand-new type of vaccine that doesn't use any part of actual virus at all. Instead, it just gives our bodies the virus's RNA (tiny pieces of genetic code) that tell our cells to produce the antigens, which then activate the immune response. No vaccines using this approach has ever been approved for use in humans. These are called as the third-generation vaccines and are 27 in race. Because they don't involve growing any part of the any virus, they can be made extremely fast. This record-breaking vaccine was a third-generation candidate from a US company called Moderna. [33,36]

But making a vaccine candidate isn't the hard part. The next phase is clinical trials. Traditionally, there are 3 phases;

- Phase 1- Where teams give their vaccines to small group of people, wait a few months and see if any of them report dangerous side effects.

If everything looks good, the vaccine moves onto phase 2.

- Phase 2- Here the vaccine is given to couple of 100 people again, to see if there are any dangerous side effects but also to see if it involves immune system ramp up. That usually involves more waiting, usually months. Then the candidate moves on to third phase.
- Phase 3-Where thousands are vaccinated to triple-check for side effects and see how well it works. That's another few months or years of waiting.

This isn't like testing the drug, giving it to people with a disease and see if it makes them better. We are giving it to people who don't have a disease and then check later that they still don't have the disease. In normal times, this whole process can take around 4 years, testing around 5000 people. But in the case of COVID-19 vaccine developers are hoping to do these simultaneously, still testing the same number of people but all in around 18 months. [34] This is how some candidates are moving so quickly like, FDA cleared the Moderna's third-generation vaccine for phase 2 trial [37] and China's "Cansino biologics" also entered phase 2 trials of its second-generation vaccinein April, 2020 [38]. Most promising vaccine right now is the one from oxford university which entered the merged phase two and three. [39]The trials stage of the vaccine race can't go any faster, for a good reason. Without going through all these trials, it would be absolutely unethical to roll out a vaccine pathetically to entire global population and can cause some real harm.

CONCLUSION

Ways to end this pandemic are existing medicines, new therapies or vaccines but the most promising one is the vaccine as stated by the experts. Almost all the aspects of COVID-19 have been clearly elaborated in the paper which comprises of major conditions caused by this disease and effect the human body in harmful manner. It is extremely important for the cure to be produced as soon as possible because not only the virus but our own immune system is also turning against us under the impact of virus. No vaccine is 100% effective, but we are expecting the one that should be able to balance the patient's immunity at an accurate level so that neither the virus overpowers the host's immune system nor the cytokine storm occurs. Not everyone who receives vaccine will be perfectly immune but vaccines don't need to be perfect to end pandemics. To wipe out an infectious disease we need more people to be immune and attainherd immunity threshold.The idea is that either an individual become immune by getting infected and surviving or getting vaccinated.When enough people are immune the virus has trouble spreading and slows down. By vaccinating ourselves we are not just protecting ourselves but also the weak in members around us who may not be able to get vaccines or whose immune system could not react effectively to vaccine like newborn, elderly and others. It is both an act of protecting ourselves and act of altruism. Along with the vaccines, the production of effective drugs against cytokine storm are also essential as it is one of the major reasons behind acute lung injury and death.

As essential, even if the vaccine or any other expected cure is fully proof by 20 months, we still have a bigger issue i.e. the mass production.

Remember, in order to end this pandemic, we need to reach herd immunity threshold and for this coronavirus, expertise estimate it to be 60%. That means 60% of appropriately 8 billion people i.e. around 4.8 billion, therefore4.8 billion people needs to be immunized in order to gain herd immunity threshold and for that, this big number of vaccines are to be produced with all safety and precautions in the record time. A vaccine can win only if it gets to billions of people, including those who cannot afford it. To vaccinate the world, we need more than one winning candidates of vaccine production. This race isn't between candidates but between humanity and virus which is just a little simple vehicle that has paralyzed the economies and ended hundreds of thousands of lives around the world.

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FIGURE LEGENDS

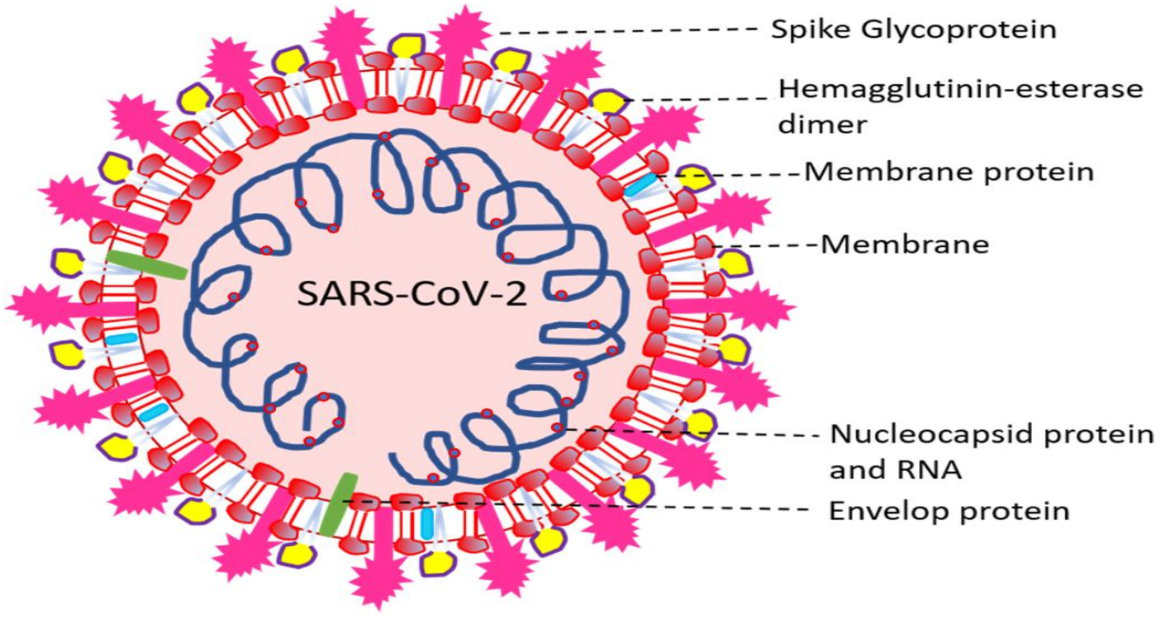


Figure-1: Detailed structure of SARS-Cov-2virus. [4]

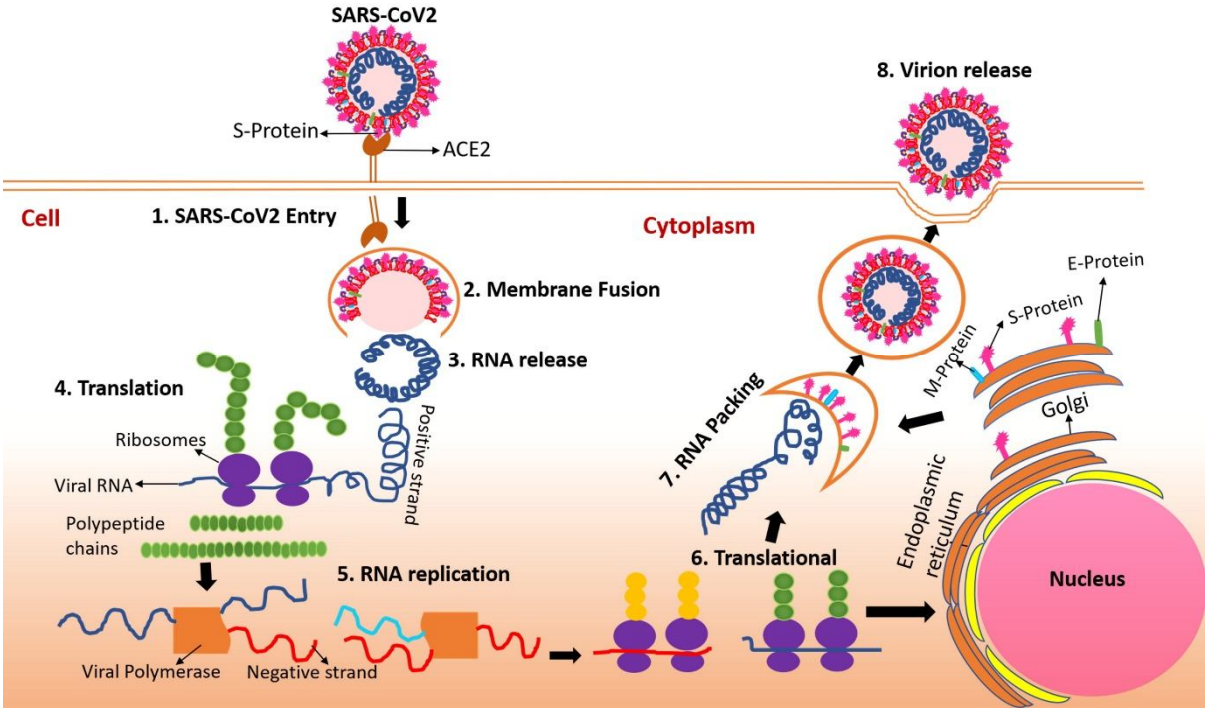


Figure-2: Pathogenesis of virus attacking and replicating inside the host cell.[4]

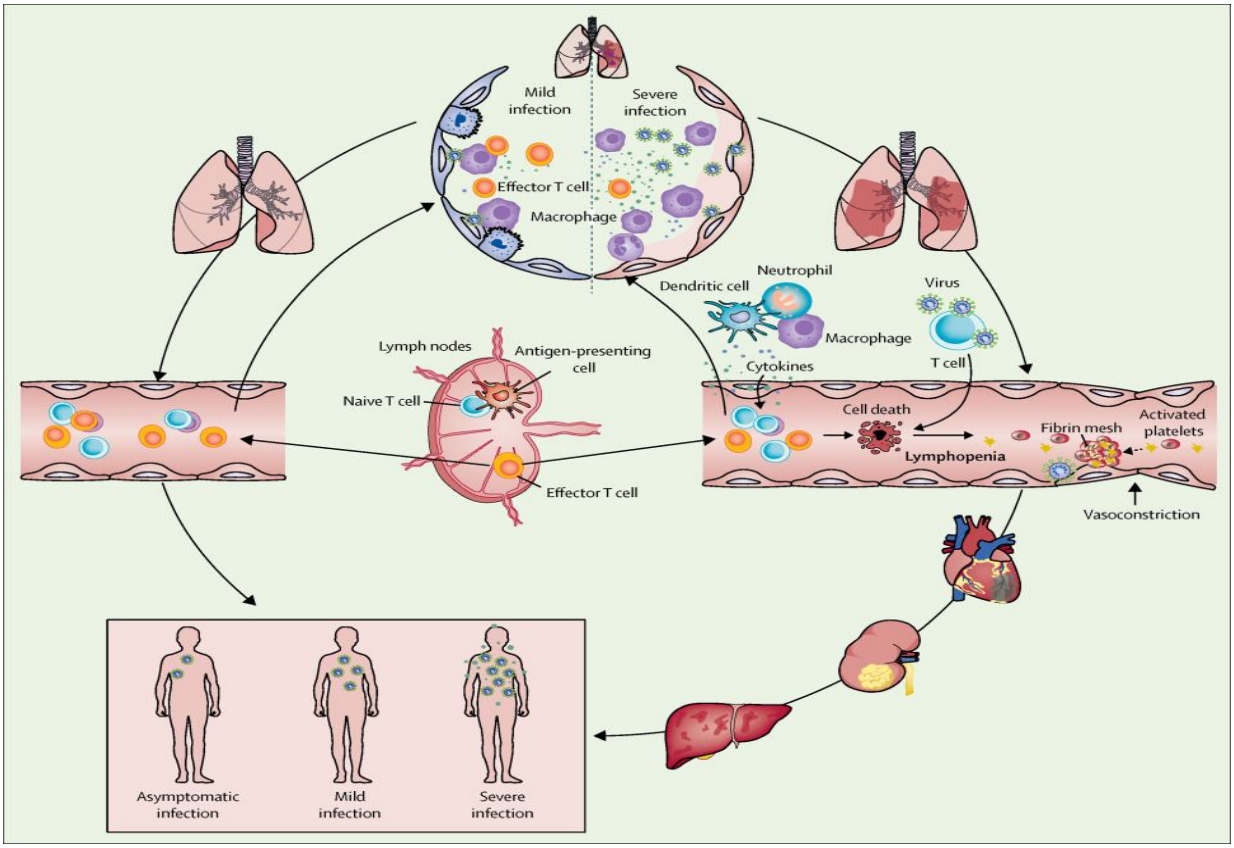
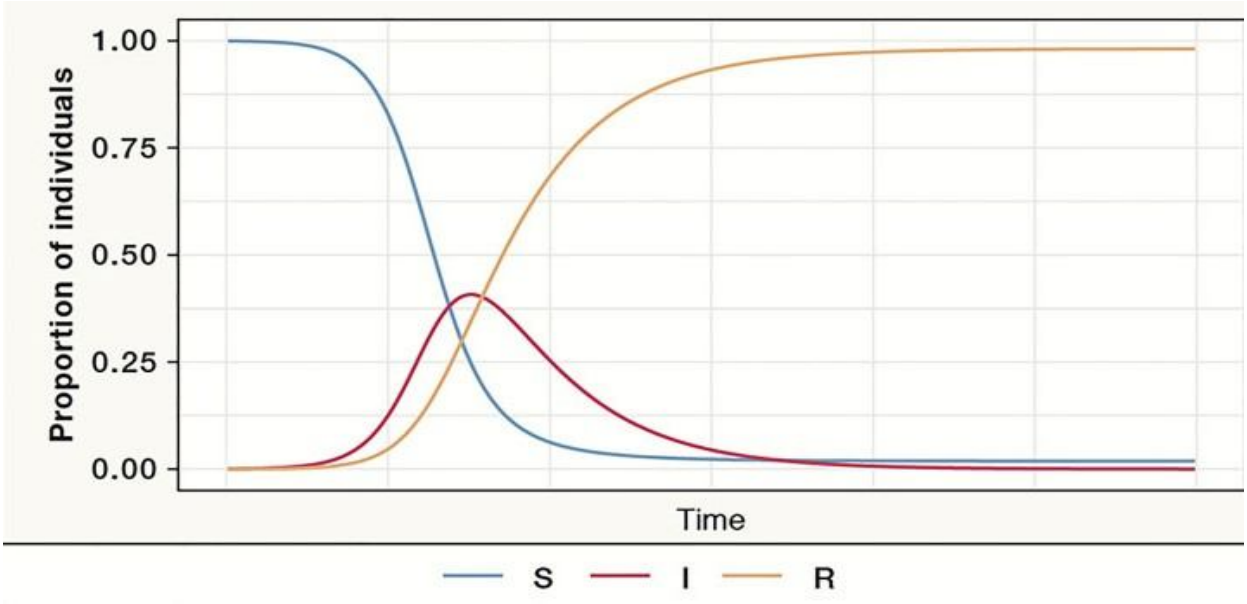


Figure-3: Effect on various organs due to cytokine storm. [35]



Graph-1: An SIR graph demonstrating the effect of herd immunity. [30]

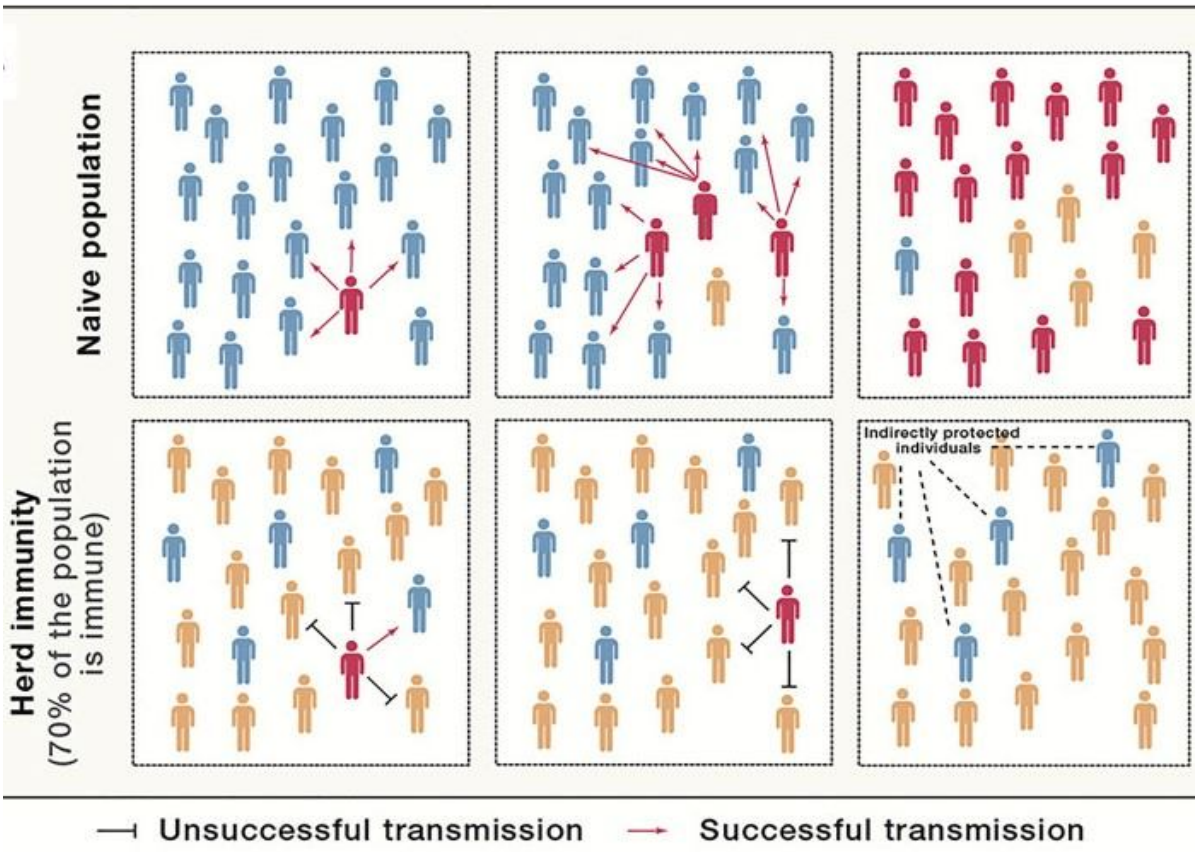


Figure-4: Concept of Herd Immunity. [30]