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Review Article

Corona Virus Generated Pathogenesis, Antigenicity, Neurovirulence, and Host Immune Responses

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Abstract

This article tries to draw attention of scientific community that coronavirus seems to be a laboratory manufactured virus. Since its outbreak in November 2020 corona virus has infected millions of people and caused thousands of deaths in the world. In a short span of 18 months, it has rapidly spread in more than 207 countries of the world. In all different climatic conditions virus is multiplying in squared numbers, with an increase in fatalities and infectivity so far. Its double and triple mutants. Virus has no effect of climatic conditions and seems thermal resistant; as it is showing almost similar mortality rate in cold countries as well as in warm countries. This is of great concern that virus is behaving like a bio-weapon, much different than any natural virus. It is mutating at much faster rate like an artificial/recombinant/superimposed RNA virus particle and adjusting sequences accordingly in variable weather conditions. Recently its double mutant strains have been detected in large numbers of patients in India in five states. Though, for prophylactic use many vaccines have been generated and their success will depend on behavior of virus because it is changing amino acids in antigenic site. It is still doubtful that existing vaccines will provide broader protection against fast spreading pandemic virus. Present paper is describing corona virus generated pathogenesis, antigenicity neurovirulence, and host immune responses. In this article few important suggestions have been given on virus transmission, pathogenesis, and development of immune responses, prophylaxis and vaccination. This ongoing Covid-19 pandemic occurred very fast and raised a political, social, economic, clinical and therapeutic issues.

Keywords: COVID-19; Pandemic; Infectivity; Mortality; Conventional Methods and Vaccine

Introduction

The coronavirus has been spreading very rapidly in all corners of the world. This deadly virus initially generate common cold like symptoms in first four days, then multiply and targets lungs and grow in upper respiratory tract. Virus heavily invade immune cells, body organs and affect the vitality of alveolar cells of lungs, the most vulnerable and essential part of the body. Virus stays for weeks in nose, sinuses and throat. But after 4 - 5 days virus establish its growth in the cells of the air passage ways and lungs as well. The disease shows mild to high morbidity that results in lethality. Covid-19 infect all four classes of human population i.e. neonates, infants, juveniles, adults and old age people. Disease targets young ones and it is too risky to neonates and immune compromised persons. After 5 to 6 days disease virus multiply very fast and causes respiratory burst and multi-organ failure. With the increase in virus replication cycles, virus load and virulence get extremely increased. In the end stage, patient develop swelling in adenoids, respiratory blockage, hard dry cough, severe pneumonia, bronchi-

tis and feel heavy breathlessness**.** Between 9 - 15th day Covid-19 become more disastrous and results in sepsis, organ system failure that cause large numbers of deaths [1].

Recent corona virus pandemic created panic and miseries. Whole world is passing though a worst phage of virus invasion and mortalities occuring in more than 207 countries, it raises few grave questions. Till the date virus has infected billions of people and thousands have been died untimely and unfortunately. Virus has mutated twice and enhanced its contagious infectivity rate well. It shows very short incubation time, high infectivity, acquiring new mutations, surviving in all weather conditions. Virus is showing immune insurgence, acute respiratory syndrome, multi-organ system failure and causing high mortality in patient. Due to all weather resistance and its fast multiplication, uncontrolled fatalities, virus seems a bio-weapon, or a laboratory synthesized artificial virus (Figure 1).

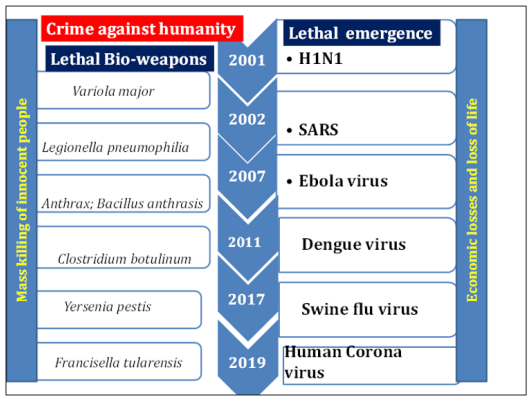

Figure 1: Showing emergence of various pathogens in a very short span of time.

People are suffering a lot; innocent people are dying unknowingly in lack of clinical care. Though vaccination is going on but it is not much enough as it will require billions of doses to vaccinate vast population. All of a sudden invisible entry of a small RNA particle has created havoc round the globe. In a very short span of time virus has infected a larger portion of civil society and caused large number of fatalities. All developed and developing countries have been targeted by the virus and it has broken economic, social, cultural and health care practices. America, Europe, Brazil, India, Southeast Asian countries and Australia are worst affected. Infection has been reached from China to Europe through invisible or unidentified route mainly by super-spreaders. Further, anthropogenic activities such as trade, transport, business, tourism and religious activities assisted this virus to spread. Virus has transmitted silently through dozens of ways and modes. It is highly noticeable human negligence ignorance, and human mistakes have increased the severity of disease. Meanwhile, super spreaders unknowingly enhanced the accidental unmanageable transmission risks in high density population zones. Virus has been largely transferred from vegetable markets, bus and railway stations, air journeys, schools, malls, hospitals and social and religious ceremonies and games.

It is fact that no single cure or treatment method is not still available to strongly fight against this virus. Scientists have generated few appropriate vaccines, and vaccination is going on. But its success will depend on behavior of virus and efficacy of vaccine. It is a time taking and will need huge resources and large scale management. One year and six months has been completed of its spread and virus has killed thousands and still pandemic is going on. Besides, prophylactic use of vaccine, all conventional methods should be used to end this virus as soon as possible to save the people. For control of corona virus pilot scale long term plan are required for abatement and completely wipe out corona virus from the human society living across the world. It could be only achieved by using all conventional, physical, clinical and therapeutic methods [2]. Since 2000 many zoonotic viral diseases have been emerged and caused heavy mortality in human beings [3-5]. This year danger has been increased as second wave evoked by mutable strains of this virus. Mass vaccination is needed for complete mitigation of Covid-19 quickly as possible (Figure 1).

This is highly noticeable that virus is causing high mortality rate as reported in cold countries where temperature is below 4 degree in Europe, and similar mortality rate is reported In India in Gujarat and Maharashtra where temperature is more than 40 degree. It has been seen first time in virus generated diseases. As general nature of communicable viruses as they show infection in particular confined geographical area. Then they reach/spread in adjoining peripheral areas and generally take year's to transform from epidemic to pandemic. But this virus has spread at much higher rate since its appearance in Wuhan, China. Corona virus is regularly changing arrangement of its genomic sequences, and enhanced its lethality against man. It creates doubt that present virus is artificial, it is not

natural one, it is a semi natural artificial virus, made at least by recombination of two other virus genomes from two animal hosts. It is a fusion of two viruses, with two mouths and no tail. It is proved by its negative and positive mutational positional analysis that indicates and shifting of few genes in genome at new locations. For providing its present shape like a natural virus, it might be cultured 3-4 years in controlled axenic conditions and kept preserved in Virology Institute at Wuhan (Figure 2).

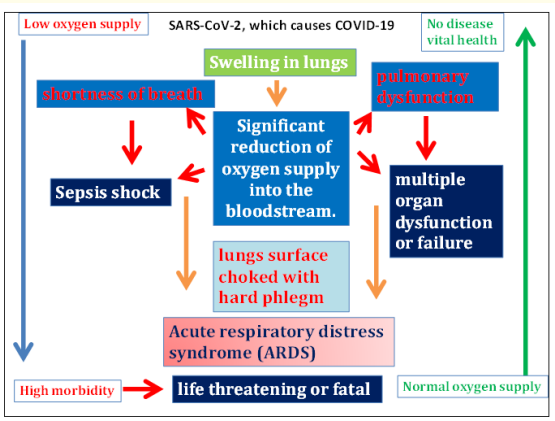

Figure 2: Major pathogenesis caused by corona virus in human patient.

This virus shows similarity to thermophilic viruses of yellow shrimps found in ocean basement in much enlarged natural habitat [6]. So far studies have been done 6 viruses found infectious in nature i.e. pancreatic necrosis virus (IPNV), infectious hematopoietic necrosis virus (IHNV), infectious salmond anemia virus (ISAV), nervous necrosis virus (NNV), epizootic hematopoietic necrosis virus (EHNV), infect spleen and kidney virus (ISKNV), Koi herpes virus (KHV) have been reported in various shrimps from South China Ocean. These viruses cause more severe infection both in marine and fresh water shrimps and cause mass mortality in them within few days [7]. Though, marine shrimps also possess low mortality causing strains of this virus [7]. Among them nidovirus is a gill-associated virus of *Penaeus monodon* prawns [8-10]. Even it is very clear about shrimps, no virus free shrimp populations found in the wild, and individual animals often carry multiple viruses [12-15].

Corona virus genome

The genome size of corona virus is largest among all the RNA viruses; it ranges from 26.4 to 31.7 kilobase approximately [16]. The corona virus genome is a positive single strand RNA; it contains approximately 30,000 nucleotides. It regulates formation of structural and nonstructural proteins of virus. It has a critical role in viral RNA synthesis. Its genomic strand on one site contains methylated cap at 5' site and a polyadenylated tail at 3' prime site [17]. Coronavirus fuse with human genome, express and replicate their genomic RNA, it makes full-length copies through replication. Its genomic organization begins with 5'-leader sequences-UTR replicase/transcriptase- spike protein (S)-envelope protein (E)-membrane (M)-nucleocapsid (N) -3'UTR poly (A) tail. Virus contains two large open reading frames i.e. ORF1a and ORF1b) at 5′ end that occupy two-thirds of the capped and polyadenylated genome.These encode the synthesis of replicase/transcriptase a polyprotein. These polyporoteins self cleaved generate nonstructural proteins. The other reading frames encode the regulation of major structural proteins i.e. spike, envelope, membrane and nucleocapsid [18].

Life cycle

AAfter reaching in the side the gut and respiratory corona virus spike proteins interact with the host cell receptor ACE2 angiotensin-converting enzyme 2 (ACE2) receptor [19]. After entry of virus into host cells by endocytosis and either by direct fusion of the viral envelop with the host membrane [20]. Now host cell protease cleaves and activate the receptor -attached spike protein. Inside the host cell, the virus particle loose coat and its genome comes inside the cell cytoplasm [21]. It's RNA strand/genome bears methylated cap at 5' site and a polyadenylated tail at 3' prime site, it permits the RNA strand to seek an attachment with ribosome of host cell for protein translation [21]. Now host ribosome translates the overlapping open reading frame of the virus genome and prepares a long polyprotein. This polyprotein has its own proteases which cleave the polyprotein into multiple non structural proteins [21].

For finding host cell, S-protein of corona viruses binds ACE-2 receptors or metalloprotease amino-peptidase N. Other Viruses, which contain HE-protein, bind on N-acetylneuraminic acid a co-receptor found on host cells. But it is not clear whether the virus gets into the host cell by fusion of viral and cell membrane or by re-

ceptor mediated endocytosis. Possibly virus may in-corporate via an endosome pathway. It may acidify by proton pumps, and chose another route to escape destruction and transport to the lysosome. Because corona virus is a single positive stranded RNA genome, it can directly produce their proteins and form new genomes in the cytoplasm. Virus first synthesizes the minus strand using the positive strand as template. Subsequently, this negative strand assists as template to transcribe smaller subs genomic positive RNAs which are used to synthesize all other proteins. Furthermore, this negative strand serves in replication of new positive stranded RNA genomes. Further, a non-structural protein assist in the replication by managing proof reading of sequences because of lack of RNA-dependent RNA polymerase [21]. All these mRNA transcripts are translated into the structural proteins and large numbers of accessory proteins by host's ribosomes [22]. A RdRp complex directly mediates the synthesis of negative-sense genomic RNA from the positive-sense genomic RNA [21]. This directly mediates the synthesis of negative-sense subgenomic RNA molecules from the positive-sense genomic RNA. This is followed by the transcription of these negative-sense subgenomic RNA molecules to their corresponding positive-sense mRNA [22]

Virus N protein binds genomic RNA and the protein M integrate into the membrane of the endoplasmic reticulum (ER) like the envelop proteins S and HE. The viral structural proteins S, E, and M move along the secretory pathway into the Golgi intermediate compartment. There, the M proteins direct most protein-protein interactions required for assembly of viruses following its binding to the nucleocapsid [23]. RNA mediated protein translation takes place inside the endoplasmic reticulum. Progeny viruses are then released from the host cell by exocytosis through secretory vesicles [23]. After binding assembled nucleocapsids form a helical twisted RNA bud into the ER lumen and form membrane to cover. These viral progeny are finally transported by Golgi vesicles to the cell membrane and exocytose or release into the extracellular space.

After replication number of non-structural protein are formed by a multi-protein replicase-transcriptase complex. This is a RNA dependent RNA protein that functions as the main replicase-transcriptase protein. More specifically structural protein, nucleocapsid protein (N), and nonstructural protein 2 (nsp2), participate in viral RNA synthesis. This protein complex assists in RNA transcription. Further, expression of the corona virus replicase-transcriptase protein genes is mediated by the translation of the genomic RNA. This replicase-transcriptase protein complex is encoded in open-reading frame 1a (ORF1a) and ORF1b and is synthesized initially as two large polyproteins, pp1a and pp1ab.

Corona virus generated pathogenicity

Destruction of lungs

Due to corona virus attack lungs are severely damaged due to over secretion of cytokines and inflammation. Patient starts feeling breathlessness or faces a problem in breathing properly. Due to over reaction of immune response and low supply of oxygen, blood vessels damaged in the war between the virus and immune system. Destruction of lung tissue, and leaking fluid into lung tissues, prevent delivering oxygen to the blood and removing carbon dioxide. This kind of inflammation and destruction that is called pneumonia. This is the specific character of corona virus that it targets lungs a very vulnerable and essential part of the body. Though virus also grow in upper and lower respiratory tract and show presence in respiratory air passageways. In beginning corona virus shows symptoms much similar to common cold typically infect the nose, sinuses and throat. Presence of virus in upper respiratory tract and nasal sacs lead its easy spread in air and help in transmission of virus. Virus comes out in watery aerosol from patient's nose during a simple sneezing. The It enormously multiply in lungs, gut and other body organs and take control over host cells it genetically and make more copies of virus (Figure 2).

Obstruction of cellular respiration

The immune surveillance cells identify virus and start its elimination when a small infection takes place. But virus replication much vigorously and cause collateral damage. A huge crowd of virus is attacked by large number of cell secreted cytokines and a big clash starts in lungs. It leads to shortness of breath and low supply of oxygen in the blood. It breaks buffering capacity of blood and obstructs cellular respiration. Fluid filled in lungs cover the breathing surface and patient forcefully tries to take 30 breaths a minute in comparison to the normal rate of 12 to 20 breaths a minute.

Respiratory failure

Patients with shortness of breath specially need oxygen ventilators. That is fitted with special masks to deliver very high concentrations of purified oxygen into the mouth, or they can be put on a ventilator. This involves placing a tube into the throat so the machine can push oxygen directly into the lungs. Such type of respiratory failure has been seen in gut associating hepato-pancre-

atitis respiratory virus infection occurred in shrimps. This virus also needs very high oxygen requirement, show high disease transmission, high morbidity and mortality in shrimps [25]. In yellow shrimps this virus grows in gills, generate sepsis in lungs, liver, pancreas, kidney and mucosal lining of gut. It causes heavy tissue necrosis of vital organs, slow down tissue respiration and imposes high morbidity due to failure of defense making immune molecules and its pathways [17,26]. Though, shrimps lack adaptive and innate immune response mechanisms (i.e., antibodies, lymphocytes, cytokines, and interferon) but they possess Toll-like receptors have which could identify this virus. Shrimps have no anti-viral immune defense [27, 28].

Attack on the kidneys

After lungs kidneys are important vital organ. Kidneys remove waste from the blood after ultra filtration. The corona virus hijacks and destroy cells of the kidney mainly nephrotubules. Heavy virus load imposes direct parenchymal infection of tubular cells with marked acute tubular injury (ATI) and erythrocyte aggregation. Failure of kidney affects plasma elemental levels that cause toxicity. It creates problem in removing of waste from the blood. (Figure 2).

Immune responses in viral sepsis

Sepsis is a life-threatening organ dysfunction syndrome. It is caused by dysregulated host response to infection that leads to uncontrolled inflammatory response followed by immunosuppression. Sepsis severely affects the function of all immune cells. Sepsis severely affects apoptosis and decrease the number of DCs, which are the most potent antigen-presenting cells (APCs). Sepsis results in impairment of innate and adaptive immune responses. Several mechanisms are responsible for sepsis-induced immunosuppression, these are apoptotic depletion of immune cells, increased expression of negative costimulatory molecules, increased regulatory T (Treg) cell expression, expression of programmed cell death (PD)-1 on CD4+ T cells, and cellular exhaustion.

Corona virus seriously effect humeral immune responses, it is infiltrate into primary and secondary lymphoid organs and delaying antigen identification, its presentation to APCs and obstructing regulation of TH helper cells, delaying B cell clonal proliferation and decreasing antibody secretion from plasma B cells. Corona virus is challenging innate immune defense mainly destroying anatomical, phagocytic and inflammatory barriers.

Virus is aggravating cytokine secretory cells mainly dendritic cells, macrophages, NK cells, and delaying formation of CTL complex.

Corona virus invasion is detected by pattern recognition receptors (PRRs) [29]. These receptors help to identify pathogen-associated molecular patterns (PAMPs) (e.g. viral RNA and DNA) and damage-associated molecular patterns (DAMPs) (e.g. host DNA and proteins) [29]. Though, several families of PRRs assist in innate immune responses, such as TLRs, cytosolic RNA sensors [e.g. retinoic acid–inducible gene (RIG)-I and melanoma differentiation–associated gene 5 (MDA5)] and cytosolic DNA sensors (e.g. absent in melanoma 2, IFN-γ-inducible protein 16, and cyclic GMP-AMP synthase) [30]. These (PRRs) receptors activate innate immune responses and the recruit leucocytes to encounter pathogens [29,30]. Innate immune responses stimulate the production of pro-inflammatory cytokines and impose an immediate antiviral effect and prevent virus spread and its replication. This effect is mainly exerted by type I IFNs [31,32]. Furthermore, PRRs also initiates development of virus-specific adaptive immunity (e.g. cytotoxic T lymphocytes, antibodies) to clear viruses and virus-infected cells [33]. Lastly, PRRs start secretion of anti-inflammatory cytokines such as IL-10 and IL-13, which help to resolve the pro-inflammatory state and promote tissue repair [34,35].

In addition, repeated attack of corona virus decrease the number of immune cells mainly those participate in innate and adaptive systems. It occurs due to excessive apoptosis causes massive loss of immune cells Few other factors, including steroids, cytokines (tumor necrosis factor [TNF]-α, high mobility group box1 protein, FasL, and heat shock protein), also try to regulate apoptosis by directly modulating the activities of caspase8 in the death-induced signaling complex or by changing the levels of death and survival factors that control the Fas apoptotic pathway. But, the release of anti-inflammatory cytokines, such as interleukin (IL)-10 and transforming growth factor beta, could accelerate apoptosis. This process ultimately leads to major consequences.

Lymphocyte apoptosis occur in the lymphoid (spleen, thymus, and lymph nodes) and other organs results in impaired immune cell activity. All important immune surveillance and defense making cells neutrophils, monocytes and macrophages, B cells, natural killer cells [NK cells], dendritic cells [DCs]) are worst affected.

These are attacked by the virus and undergo the immunosuppressive phase of sepsis. Early activation of both innate and adaptive immune response is involved in the pathogenesis of sepsis. To overcome the infection virus and to neutralize the antigens overwhelming inflammatory response, mass release of cytokines or "cytokine storm," occurs. This generates high fever, refractory shock, inadequate resuscitation, and cardiac or pulmonary failure. Meanwhile, mortality at the later period is due to persistent immunosuppression with secondary infections that results in organ injury and/or failure. Thus, sepsis creates a lethal stage of all round attack and cellular death caused by pathogens and host immune response, where the pathogens seek an advantage by incapacitating various aspects of host immunity. Large number of patients affected with sepsis showed unresolved opportunistic infections and immunosuppressive features.

During apoptosis, pro-inflammatory cytokines release is inhibited, but the secretion of anti-inflammatory factors get activated, it shows a shift from T helper type 1 (Th1) to Th2 cytokine production. T_H1 cells and CD8 T cells cause apoptosis of virus infected cells and activate production of reactive oxygen species in phagocytes that kill the virus. Further, sepsis induces functional and quantitative changes in immune cells that results in lymphopenia, and slow progression of immune paralysis. Besides, a non-type 1 cytokines also operate to make an inappropriate type 2 or type 17 immune responses that simply cause inflammation but cannot clear the virus. This over activation of immune response causes massive loss of immune cells because of excess of apoptosis. Further, this uncontrolled apoptosis of immune cells result in immunological intolerance. For example, the depletion of macrophages and NK cells impairs microorganism clearance, which leads to protracted inflammatory responses.

Due to repeated cycles of virus replication, virus genetics seek control over host cells and reprograms it genetically to make more copies of virus. Then it begins its attack. Virus start dislodging alveolar cells and a watery viscous liquid seeps in the lungs, that later on precipitate become thick and dry to form hard layer of sputum on lung alveoli. It severely affects lung function and sputum chokes tiny air sacs, and prevents them from delivering oxygen to the blood and removing carbon dioxide. It is this kind of inflammation and destruction that is called pneumonia. Blood vessels also get damaged in the war between the virus and immune system. In this stage severely ill patients display shortness of breath and low levels of oxygen in the blood. It could be confirmed by Chest X-rays and CT scans by thick white spots in lungs. Such patients usually breaths 30 times in a minute or well above the normal rate of 12 to 20 breaths a minute and need high oxygen supply. On ninth day onward antibody production is elevated, resulting in opsonisation, greater phagocytosis and destruction of viruses. Virus is cleared and memory T cells are produced, which can rapidly respond to future infections.

Septic shock

In septic shock immune system is trying to attack the virus everywhere. This overreaction causes severe inflammation and damages human cells throughout the body. This is a natural process that is usually triggered by any severe infection. Due to oxygen deficiency organs can start failing. Virus heavily invades lungs and kidneys, and creates septic shock. This multiple organ dysfunction syndromes (MODS) a sever stage of physiological distress increases with the physiologic derangements in individual organs; it is a combined process rather than a single event. Alteration in organ function occurs from a mild degree of organ dysfunction to completely irreversible organ failure. This Severe Acute Respiratory Syndrome generated by corona virus 2 (SARS-CoV-2) causes heavy septic shock in immune compromised patients with severe pneumonia. Organ dysfunction puts a major clinical impact on patients mind.

Antigenicity

Corona virus surface proteins such as S protein, S2 protein, spike protein, IL-8, S, N, and M, Proteins, S and N proteins. These are important antigens mainly membrane glycoprotein, envelope protein and nuclear capsid protein bind to specific antibodies in vitro. Though, new B cell epitopes could be searched by using antibody binding with high affinity. Few important corona virus (COVID-19 S2) antigens are Spike RBD antigen-His, biotinylated COVID-19 peptide antigens. Other common human CoVs antigens are HCoV-OC43, and HCoV-HKU1 (betaCoVs of the A lineage); HCoV-229E, and HCoV-NL63 (alpha CoVs) recombinant antigens are most commonly used. These antigens are also detected in common colds and self-limiting upper respiratory infections in immune-competent

individuals. Other human CoVs: SARS-CoV, SARS-CoV-2, and MERS-CoV are betaCoVs of the B and C lineage, respectively. These also show extra-respiratory clinical symptoms. Both strains showed the mortality rates up to 10% and 35%, respectively.

Spike proteins are the visible protrusions on the surface of SARS-CoV-2, which give the virus its characteristic, crown-like appearance. S1 and S2 are homotrimeric proteins which are heavily glycosylated, and form two distinct subunits. It contains immune dominant region between amino acids 510 to 672 [36]. Spike protein act as a molecular key, and specifically bind to specific ACE2 cell-surface receptors present on the host cell surface. Spike proteins are exposed to local environment and recognize the immune system. Spike protein is immunodominant corona virus antigen that elicits a strong neutralizing antibody response [37]. It is highly antigenic in nature and is used in diagnostics and vaccine development. There are two major types L and S types of SARS-CoV-2 virus strains; these show two SNPs that show nearly complete linkage across SARS-CoV-2 strains. Although, the L type (~70%) is detected in most cases than the S type (~30%) in the SARS-CoV-2 viruses. Both might have different antigen sets but S protein in both has similar role [37]. Key receptor proteins and their role in virus infection and disease evoking have been mentioned in Table 1.

Target candidate	Full name	Role during viral infection	Drug target
ACE2	Angiotensin-converting enzyme 2	A viral receptor protein on the host cells which binds to viral S protein	Arbidol
AT2	Angiotensin AT2 receptor	An important effector involved in the regulation of blood pressure and volume of the cardiovascular system	Arbidol
S protein	Viral spike glycoprotein	A viral surface protein for binding to host cell receptor ACE2	Arbidol
S1 protein	Viral spike glycoprotein	A viral surface protein for binding to host cell receptor ACE2	Arbidol
S2 protein	Viral spike glycoprotein	A viral surface protein for binding to host cell receptor ACE2	Arbidol
3CLpro	Coronavirus main protease 3CLpro	A protease for the proteolysis of viral polyprotein into functional units	Lopinavir
PLpro	Papain-like protease	PLpro a protease for the proteolysis of viral polyprotein into functional units	Lopinavir
RdRp	RNA-dependent RNA polymerase	An RNA-dependent RNA polymerase for replicating viral genome	Remdesivir, ribavirin
TMPRSS2	Transmembrane protease, serine 2	A host cell-produced protease that primes S protein to facilitate its binding to ACE2	Camostat mesylate
N, and M	Membrane glycoprotein, envelope protein and nuclear capsid protein	Assist in virus replication	Camostat mesylate

Table 1: Key receptor proteins and their role in virus infection and disease evoking.

An inhibitor of viral entry to host cells. Its direct action on S protein and ACE2 is yet to be confirmed.

Neurovirulence

Coronavirus generated neurovirulence is not well understood at the molecular and cellular layer. This virus come across the BBB and induces proinflammatory signals from brain cells for the recruitment of blood-derived inflammatory cells [38]. Corona virus

is potential neurovirulent (Ni) pathogen it targets central nervous system (CNS), it targets nerve cells and other parts of brain. Virus propagates itself in neuronal cells causes neurovirulence and CNS pathology [39]. It shows high neurovirulence than encephalitis, meningoencephalitis, and meningoencephalitis viruses [40]. Virus attaches to airway epithelia and grow inside alveolar cells, virus reaches to nasal sacs, and from where pass into olfactory lobes that to find way into CNS via neuronal contacts with the recruitment of axonal transport. Here, it infects neuroglial cells and neurons and cause cell death like encephalitis virus [41]. Virus imposes immune-mediated demyelination that more rapidly occurs than fatal encephalitis [42]. Besides, neurovirulence, neurotropic viruses also severely affect CNF function mainly cerebellum.

Brain possesses structural units like endothelial cells, pericytes, and neurons. After having infection these secrete proinflammatory cytokines which signal, astrocytes and microglia and communicate. Inflammatory cytokine infiltrates from 2 to 3 days after infection, peak at days 5 to 7 after infection. These gradually decline over the next week. Virus induces proinflammatory cytokines (interleukin 12 [IL-12] p40, tumor necrosis factor alpha, IL-6, IL-15, and IL-1β) in astrocytes and microglia in mice brain and spinal cord. Corona virus antigens have been detected in specific locations in the brain, especially in areas associated with the olfactory and limbic systems [43,44]. ACE2 receptors also found expressed in glial cells and neurons, which are potential targets of COVID-19. P SARS Co-V invades the brain via the nose close to the olfactory epithelium [45]. Virus causes neurologic manifestations in cerebrospinal fluid and obstructs involuntary control over breathing [46].

Disease transmission

Man to man transmission

Covid-19 virus is different in mode of transmission than other viruses. Virus is directly transmitted from diseased or infected human being to uninfected human being and transfer from animal to human by pets and wild animals. Virus is easily transmitted from aerosols and sneezing droplets released from respiratory droplets nose of infected person in coughs or sneezes. Virus also moves with the wind according to its direction. Therefore minimum distance for safety from corona virus is 2 yards or person to person distance should be at distance of less than 6 feet. These droplets enter inside nose through nostrils of individuals and then inhaled to lungs. Moreover, Infection can be made by contaminated surfaces or objects according to reports of CDC. Corona virus is highly infective, pathogenic and dreadful virus.

There are many animal species which are natural host of many human disease causing viruses. But corona virus transmission has three possible routes; it reached into human host through food chain by flesh eaters mainly carnivore; second through association of wild animals to pet animals mainly livestock, cat and dog or pet birds; and then finally transferred to human host. The third possibility seems to be, its direct spillover from laboratory by accidental mistake [47-49]. Generally human corona viruses are spread by bats, camel and civet cats. There is a possibility humans might have received this virus after direct exposure to civets (SARS) and camels (MERS) as it was found in middle east countries. Because this new virus has no past history, it suddenly appeared as a devil and invaded large section of human society. According to genomic studies genetic re-organization of virus RNA is possible that can enhance host range, transmission and infectivity. It indicates there should be an intermediate host more likely between bats and humans [50]. It is also a fact that this newly emerged virus is behaving like an artificially manufactured virus.

Bats to man transmission

Bats are important wild vectors of corona virus, from studies more than 63 corona viruses have been isolated from different species of bats belong to 18 families. But there is evidence available that viruses are transmitted from bats to other animals. But corona virus transmission is mush similar to rabies virus and related lyssaviruses, Nipah and Hendra viruses, where other vectors spread the disease except SARS-CoV-like virus of bats. More often, bat and virus relationships has been established all different hosts other than bats and to zoonotic human diseases are not but much cleared. Possibly, viruses like alphaviruses, flaviviruses, and bunyaviruses, may infect bats via arthropods, but it is not established so far. But it is clear that bats are important reservoir hosts for these viruses. Fruit bats (flying foxes) are natural hosts or reservoirs of Hendra virus. Other transmitters of this virus are black flying fox (*Pteropus alecto*), gray-headed flying fox (*P. poliocephalus*), little red flying fox *(P. scapulatus*), and spectacled flying fox (*P. conspicillatus*) [51]. These naturally make “spillovers” in spatial and open geographical

ranges in specific locality during a limited time period. Corna virus outbreak depends on frequency of visits made by susceptible fruit bats or flying foxes during night time and virus spill in open air or cut marks onto fruits through saliva in particular area [52,53].

Transmission breakage

The natural reservoir host of SARS coronavirus (family: *Coronaviridae)* is *Rhinolophus sinicus* (Chinese horseshoe bat) is its host. Normally bats have been evolved much earlier than man and might develop both innate and acquired defense against these viruses. It is assumed that as reservoir host bats have developed immunity against corona virus and their immune system respond to virus accordingly. Perhaps their immune system might synthesize antibodies to neutralize virus that may control virus replication. More specifically, bone marrow of Indian flying foxes *Pteropus giganteus* possess surface Ig on Macrophages, B- and T-lymphocyte-like cells, and other immune cells [54]. Presumably in bats, the generation of high-titer IgG requires two steps mainly mediated by helper T cells: class switching and affinity maturation. These IgG antibodies are used in serological assays to detect Hendra virus, severe acute respiratory syndrome coronavirus (SARSCoV)-like viruses, and Ebola viruses in bats [55,56,57].

Management of pandemic

How to control human fatalities

Virus has brutally killed thousands of innocents; humanity is in tears as sudden demise of dears and near ones have been heavily jolted families, societies and communities. Terror and panic created is hovering everywhere much similar to a war scenario; as thousands of people mainly health care providers, hospital staffs, police and defense personals, civil servants, daily wagers, and common people have been died or untimely gobbled by this China made deadly virus. Virus has challenged the microbiological, genetic, molecular biology, pharmaceutical, immunological and biophysical researches of the world. Even top research institute of the world could not find able to check the devastation caused by Covid-19 pandemic as no single drug was found successful against this deadly virus. A tiny piece of virus has ruined the economy, seized the growth of world trade and business, severely affected education, research and travel, recreation, leisure and living of people at global level. It is true economic losses are repairable but people trenched to death will never come and losses are irreparable.

Recent pandemic has disclosed all truths and gaps which exist in the field of medical science and our dependence on clinical and health care systems. Truth is that many powerful countries have made atom bombs and weapons of mass destruction but do not have deterrence to control corona virus. It astonishes all of us that global research could not explore any timely solution to control this deadly virus. Now question is who is responsible for all deaths, human sufferings and huge devastation caused by recent pandemic. Answer is very simple it was originated in China and spread from there as a disastrous pandemic. It must be discussed in legal frame work in UN Security Council, WHO and other world forums with immediate effect to protect humanity on earth.

China is solely responsible for spread of Covid-19 pandemic. This is dark side of a state sponsored crime and ghastly act of Chinese government. They have denied to give realistic epidemiological data related to this corona virus and never accepted their negligence. Chinese government is highly insensitive to their own people, and same has been played with others. It is fact that PLA has crushed the civilian rights in China since long past but they have shown brutality on their own people during the pandemic period. Behind the curtain thousands of people are missing or brutally killed by army personnel's in the name of mitigation and control of this virus. People have no right to live, nor they can share information among them, press and print media has only limited rights and government agencies always broadcast favorable doctored news. Chinese Government is working on a hidden agenda i.e. invade, enhance imperialism, self centered, never bind to any rule, irresponsible to humanity, causing economic loses and killing wild animals and living beings. They are practicing uncontrolled development at the cost of nature and humanity.

Innocence and negligence

It is very clear that states did not give due attention in beginning when this virus was entering inside their mega cities through known and unknown carriers unknowingly. It was a silent entry of virus in Europe and America. It is a reality that states paid more attention to economic safeguards and trade floatation rather than their keen attention to recognize and aware about devastations caused by this deadly virus when it was spread in China and has shown mass mortality. Every fact related to epidemiology of this virus is hidden by China, and they have never revealed truth, the reasons are very clear, political and economic. This virus has been

nurtured under a communist political thought, and generated for defense use by PLA for imposition of a secrete non-army war against enemy states. Behind construction of this artificial virus, economic reasons seem to be attached as virus can be used as a non-military warfare and will curve down the huge military expenses. China is working in direction to destroy or slower down the economic development in rest of the world. It has territorial boundary disputes with 11 neighbor states and long trade rivalry to developing and developed countries. China cleverly gave a grave set back to world economy and fabulously imposed a war against humanity. This is a secret agenda on which China is working and started a non-military cold fight against democratic world. Communists thought is to conquer the world any way; by using cruel tactics; even they never hesitate to show cruelty against their own people. It is highly shameful that China has tried to hide every fact about this deadly disease that has killed millions of innocent people round the globe. In communist party ruled China; people's rights have been fully seized and caged forever. All those who tried to make this pandemic public and given videos to international media have been either perished or placed in jail and given mental and physical torture. China government and PLA is playing with the feelings of human and crushing the humanity.

How to break the chain

For breakage of transmission chain separation of infected from un-infected persons is highly important. It will need mass testing and clinical care. To stop rising number of COVID-19 cases, use of common public amenities and hospital beds, buses, trains and market places must fully sensitized. There are so many steps where special checking be required i.e. discharging the general patients without testing, analysis of corona reports, shifting of corona patients in general wards, and providing dead bodies to family members. This is the main reason that corona virus is largely targeting such human habitation with high infectivity and high mortality. Social distancing norms should be followed in aero planes, coaches of trains, buses and hiring taxies. More severe man to man transmission during close door air circulation systems is controlled. Due to close proximity of infected asymptomatic patients infection is silently transferring to healthy groups. That is why human mistakes have seriously increased virus transmission, by both direct and indirect routes, or infection evokes after hospitalization of patients. All hospital staff ward boys, sweepers, nurses, technicians and other clinical staffs, medical doctors, security personals should be tested after 14 day interval. Due to their public services are bound to dutifulness and working without PPE kits, protection wares and unsafe living places increases the severity of infection where infected patient load is very high. This is the reality that due to over warden, health care workers, doctors, and nurses are over exhausted and living under fear and trauma. This is hard fact that hospitals are running in extreme shortage of staff and high quality health care equipment's and shortage of medicines. Lockdown is way to maintain social distancing, but it is prove costly for the public and economic reasons stakes to add high infectivity and more fatalities may occur in coming months. Government has forced to open lockdown because of heavy economic downturn.

After community spread the breakage of chain is not so easy to stop transmission of this highly contiguous virus in near future. But it could be possible by two important ways; first cut down virus transmission by genetic locking or switching off virus spike protein genes in genome. It will stop making climate induced genetic variabilities mainly mutations in virus. One host receptor binding is obstructed both infectivity and mortality could be stopped. Second it is possible by using advance technology; for clinical care and proper monitoring of Covid-19 patients. Control of corona virus is possible by using all conventional, physical, clinical and therapeutic methods. The recovery rate of patients beyond 85% could be achieved due to application of such methods**.** People should obey rules of lockdown honestly, cut down their unsafe movements at public places. Increase the strength of diagnostics to short out infected from uninfected patients. Quarantine and precautionary measures such as health, hygiene and sanitation can control virus infectivity in vicinity of people. More important is to stop second wave ant how for complete mitigation of this deadly virus.

Virus generated epidemics need real time surveillance and assessment of epidemiological data and timely inaction of prophylactic measures [58,59]. There must be a long term strategic action plan for controlling the emergence of new virus infection in future (Figure 3). For fast action and find desirable success genetic, climatic and geographical mapping be needed. These threes factor trigger the spread of virus epidemics [60]. By mapping vulnerable weather parameters, it will help classify the risky geographic areas in not only in India but also in other countries. By analyzing genetic and immunological susceptibility in population groups; it will help to manage weather induced risks of virus well before the spread of

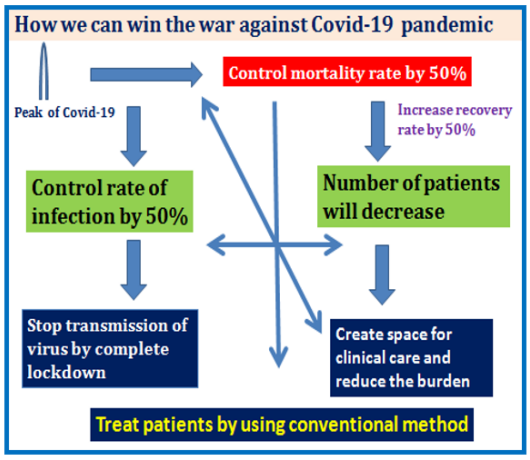

Figure 3: How to win war against Covid-19 by using conventional methods.

a new virus and it become apparent in particular geographical area [61]. Seasonal alterations in temperature and absolute humidity make conditions more vulnerable and support pneumonia infection and deaths [62]. All such problems could be solved when current data is matched with epidemiological data of past epidemics.

Early therapeutics may reduce fatalities

For better cure and clinical care early diagnosis and treatment is highly required. Though, so many vaccines are available for long term protection against this virus. But for treatment of mild patients and increasing the immunity level all possible therapeutic methods such as plasma and antibody therapy, anti-viral drugs, molecular and genetic medicines, plant natural products, homeopathic, Ayurvedic, Unani, Shiddha, alternative and complementary medicines and conventional methods should apply for instant control of this virus. In addition, fast acting physico-chemical methods which could help people to disinfect themselves are to be explored for decreasing the infection rate and increasing the sustainability of infected patients. The best way is to use of herbal quaths, concoctions and herbal karha, white alum [63], honey, and Ayurvedic bhasma. All these can be used for immunity boosting and find peripheral protection from corona virus generated morbidity (Figure 2). Inhalation of hot steam distillate and gargles help to cut down virus load in lungs and nose [64]. Thermal inactivation of corona virus is also possible by using hot 1.5% salt water or by direct thermal heat [65,66] as it is generated in thermal-aroma-carbon therapy [67].

How to solve the problem

No concrete therapeutic method and medicine is available for corona virus generated infection. Therefore, major role of social distancing, use of masks and isolation are key methods. By making people aware about causes of virus transmission, can slow down rate of infection and better therapeutic can increase the recovery rate beyond 85%. Few herbal homemade formulations are proved much better against cough, sneezing and body pain. However, this is much advisable that government should declare use of conventional methods for the treatment of mass number of patients (Figure 4). All different Ayurvedic preparations should be launched by Ayush ministry to public and these should be essentially provide to all age groups near hot spots and buffer zones to boost up their immunity to avoid ongoing deaths instantly. This is time when diagnosis of large numbers of people is a major task; further mass vaccination of all age groups will take time. Hence, self regulation must be maintained by every one of us to reduce the virus infection. Mild patients should treat at home to cut down over burden on hospitals and concerned facilities. The main problem is to manage vaccine and oxygen supply in all states. Vaccines have been generated by various laboratories against corona virus but for speedy production and restoration of supply it will need huge economic resources [37]. But it's easy availability and efficacy is still doubtful because virus is highly mutating and changes its regulatory genes according to chemical, physical and biological environment (Figure 3). An unknown fear is how long we will remain safe under umbrella of a vaccine and its immunization. The major problem is genetic instability of the virus, and acquire new mutations has raised the question regarding vaccine efficacy. Failure of vaccine may increase fatality rate. The main danger is reverse transformation of a denatured vaccine strain into virus strain if it happens, will pose a toughest challenge. There must be a long term strategic action plans for controlling the emergence of new virus infection in future (Figure 5). There is another hope i.e. development of natural resistance by generation of antibodies within body against this virus in exposed persons. But for generation of heard immunity in human population against corona virus large population approximately 87% gets exposure of this virus. For instant regulation WHO guidelines should followed very strictly to stop disastrous pandemic.

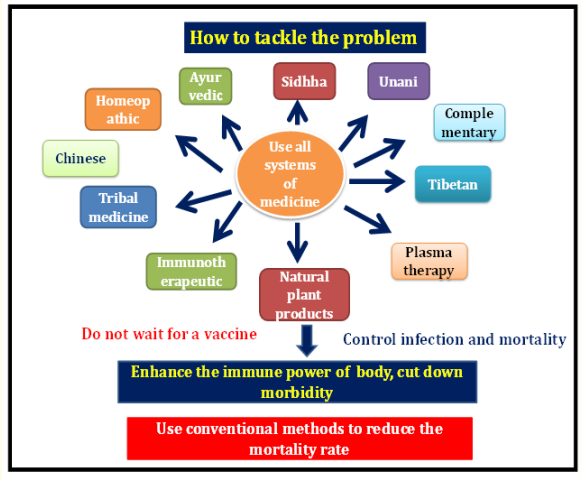

Figure 4: Showing immunity boosting medicinal systems can be used for control of corona virus infection.

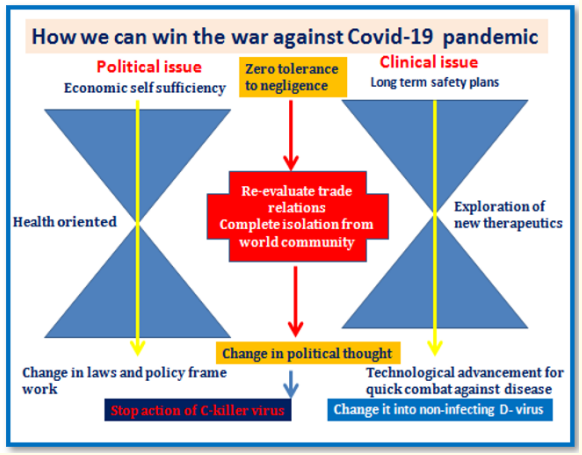

Figure 5: Showing strategic action plans for controlling the emergence of new virus infection in future.

Therapeutics and prophylaxis

Vaccination is going in different countries; most of the vaccines are RNA, peptide or recombinant vaccines. Vaccine development needs huge resources, quality control and supply according to demand. From surveillance it has been reported that vaccines are working more efficaciously and producing appropriate levels of immune response. Though, there are possibilities to have a combine antigen antigens based single vaccine, it will provide a long term safety and protection cover. Conventional vaccine approaches have not been as effective against rapidly evolving pathogens like influenza or emerging disease threats such as the Ebola or Zika viruses. But in case of corona virus RNA based vaccines showing better efficacy. RNA based vaccines need shorter manufacturing times, greater effectiveness, relatively quick and inexpensive in comparison to other vaccines. For better safe guard against virus vaccine policy, license and market policy must be improved. Vaccine must make tax free and easily licensed. RNA vaccines are faster and cheaper to produce than traditional vaccines. RNA based vaccine is also safer for the patient, as they are not produced using infectious elements (Figure 6). Production of RNA vaccines is laboratory based, and the process could be standardized and scaled, allowing quick responses to large outbreaks and epidemics. Most current research is into RNA vaccines for infectious diseases, and so many they have been launched and some are passing through clinical trials. Synthetic peptide vaccines of this conserved region were found to neutralize viral infectivity against a number of different influenza type and sub types.

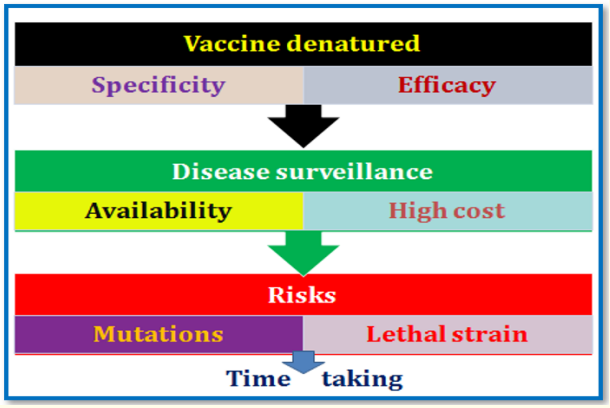

Figure 6: Important attributes of a successful vaccine against corona virus.

Conclusion

For instant regulation and quick control of corona virus pandemic disaster mass vaccination of people is essentially required

but it is a long term economic and clinical affair. To strengthen fight against corona virus emergency funds, medical aids, services, information sharing, institutional researches and technological advancements and new federal rules are to be improved and launched. All trade and traffic norms, rules and federal laws must be revised and modified to break the chain at national and international level. All international rules should be followed by every citizen, groups, community, regions and nations to protect their people and only allow safe participation in business and cultural relationships. Those who do not come in support they must be boycotted from world trade, travel and international relationships. At any level carelessness and negligence of people to follow safety protocols should not be forgiven and take very easily.

Due to sudden outbreak of virus biggest challenge emerged is shortage of PPE kits and hospital appliances and diagnostics. Current biggest challenge is to fulfill demand and supply of *in vitro* diagnostics, potential pharmaceutics, and development of rapid diagnostics, serological assays and appropriate high efficacy vaccines to stem the spread of this disease and provide long term protection cover to entire human population. At diagnosis level rapid testing of corona virus is biggest challenge because antibody testing is not much reliable test and increasing the confusion and suspicions to diagnosis as whole exercise could not give confirmatory report to exclude SARS-CoV-2 infection or to inform infection status. Hence, there is an urgent need to find appropriate and comprehensive tests of high precision level based on ranges of corona virus antigens mainly RT-PCR. Recent challenges are coming from virus genetics, as new mutations and genetic variations are emerging in corona viruses. These possess different antigen sets and show binding variability to host cells. Mutant variants of corona virus possess different amino acids in its epitopic spike protein a key residues in the receptor binding domain (aa ~450-510) that binds to host ACE2. For example corona virus strains, such as corona virus HKU1, NL63, OC43, or 229E possess spike proteins with slight differences but high antigenicity changes. There are antigenic differences in spike proteins of SARS-CoV and MERS-CoV. Both have evoked nearly in similar time schedule but in different climatic conditions. Virus seems much tolerant to temperature. Variability in transcripts, post-translational modifications of virus proteins, and shifting of amino acids in epitopes providing different protein conformation, that affects antigen binding. Most challenging task is epigenetic changes and lateral transfer of genetic material. RNA, antigens are also present in the respiratory tract of infected individuals and can be used to diagnose acute-phase infection.

Another most severe challenge is to fight against ARDS (Acute respiratory distress syndrome). It is a stage when entire lung is filled with watery mucus fluid, it soon precipitates and make a cover on elastic air sacs (alveoli). The fluid keeps lungs from filling with enough air, but lower down oxygen assimilation rate and supply much less oxygen to bloodstream. This deprives normal oxygen supply to organ systems and cells. Patient feels severe inflammatory-induced lung injury, there is a decrease in oxygen saturation (<93%). For maintaining oxygen level, oxygen incubators or protective mechanical ventilation are required more in number to mitigate hypoxia and to maintain PaO2/FiO2 parameter in artificial viable mode respiratory supply of oxygen. To overcome clinical there is a need to arrange intubation and protective mechanical ventilation to manage quick respiratory failure, including protective mechanical ventilation and high-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV).

The biggest challenge to clinical sciences is to protect immunocompromised patients and the elderly, with sever lower respiratory tract infections. Major challenges are to control pathogenicity, sepsis, multi-organ failure and high mortality rate caused by SARS-CoV and MERS-CoV. Another challenge is to diagnose the sorting patients by using RT-PCR for providing an early supportive therapy and clinical care. For protection of all age groups mass vaccination of people is highly essential to finish coronavirus from the human society across the world. It will need potential all kinds of vaccines, free of license and low cost. Besides, the patients all conventional, physical, clinical and therapeutic methods are also used to for mild patients. More important is to stop second wave of this highly mutable virus and its complete mitigation must be done as quickly as possible. Health organizations coordinate information flows and issues directives and guidelines to best mitigate the impact of the threat. This new virus seems to be very contagious and has quickly spread globally. World governments are at work to establish countermeasures to stem possible devastating effects of new mutant strains of corona virus. There is an urgent need to give up uncertainties and rumors regarding vaccines, these are only remedies which could provide protection cover against this deadly virus. Mass vaccination will need immense cooperation among states, people and society. All clinical, legal and trade issues must

be resolved to save the humanity. All overseas and foreign citizens should be registered and put inside quarantine centers with strict rules. To save the humanity on this planet, virologists and immunologists, clinicians, pharmaceutical industries and world leaders come together to enhance the vaccine production and assist in providing all time vaccine cover against any future virus attack.

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Conflict of Interest

The authors declare no competing financial interests.

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Volume 4 Issue 6 June 2021