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Deciphering COVID-19: A Review on Efforts of Life Science in Sustaining Life

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Abstract:- One of the most terrifying words nowadays is COVID-19 (short for Corona Virus Disease-2019) even more devastating is its effect on the total world where people are still shocked under its killing spree. The rate of mortality and the number of cases is going skywards, with no sign of respite. In this 21st century era we are at an advantage because of the different technological advancements at our disposal. Scientific discoveries and innovations are increasing along with it the viruses are also evolving which is one of the major concerns in today's world. In this paper we will try to peep deeper into the COVID-19 and epidemiology that should be known relating to it. The science behind its replication and virulence efficiency has been dealt at some length along with transmission efficiency. Favorable conditions required for the virus' replication has also been discussed to some extent. More emphasis has been given to explain the anti-pandemic strategies, which explain how to curb its spread and the different mechanisms that are explored to treat it. Multiple drugs and vaccines that are undergoing trials have also been presented by us. This paper is our conscious bit of effort to put some stress on making people aware of the seriousness of the matter at stake and deciphering Coronavirus.

Keywords:- *Recognition COVID-19, Epidemiology, virulence proteins, a new approach on vaccine and BCG study, transmission serial number, anti-pandemic strategies, eINDs, plasma therapy, LOCKDOWN.*

I. INTRODUCTION

Viruses are the most simple in structure yet very much complex in nature where they replicate in the host cell by transcribing and translating, very easily. The most striking feature of a virus is that it can swiftly take on the host's immune system and have a tight grip over the host's defense system. Corona virus, which has been recently named as COVID-19 by WHO has been termed as a novel virus with no previous known identification and unusually high rate of contagion rate. But this virus strain has very much striking similarity of around 96% with the SARS CoV strain which was the reason of a SARS (Severe Acute Respiratory Syndrome) outbreak way back in 2003 appearing in China and affecting 26 other countries with more than 8000 cases.[3] According to the WHO website, during the time of penning this article the virus has already spread to affect 213 countries with 19,18,138 confirmed cases of which 1,23,126 have been deceased.[1] With these figures in mind we can clearly understand why this is called a global pandemic crisis. Coronaviruses are an enormous group of infections with some causing less-serious ailment, for example, the normal cold, and others causing progressively extreme ailment, for example, Middle East respiratory disorder (MERS) and Severe Acute Respiratory Syndrome (SARS) corona viruses.[5] They have a high transmission efficiency as it can easily spread via airborne suspended nasal droplets. It has a liking for a cold weather and survives in relatively low humidity. Diagnosis is mainly through Nucleic acid hybridization test (including PCR) and ELISA. Owing to having a novel status there is yet a vaccine or drug against it.

II. MATERIALS AND METHODS

In our effort to pen down this review article we have spent a great deal of time strenuously and carefully reviewing other articles, journal, newspapers and mass media. It is in this way by considering and analyzing different view point we have put forth our views in this review article.

- *Recognition and epidemiology of 2019nCoV.*

SARS CoV-2, which is a novel corona virus isolated from Wuhan China was 96% sequence identity with SARS CoV, which was discovered in 2003. Human Angiotensin-Converting Enzyme 2 (hACE2) is the only receptor for binding of SARS CoV-2 S protein (spike protein). This binding helps the virus to fuse into the human cell with this receptor on its cell surface by endocytosis. SARS CoV-2 S protein shares 76% sequence identity with the S Protein of SARS CoV and is much unstable than SARS CoV. This spike protein (s) is the major target of antibodies for neutralization to binds its receptor and mediates membrane function and virus entry. hACE2 Human Angiotensin-Converting Enzyme 2 a type I membrane protein, is the enzyme protein attached to the outer surface of cells in the lungs and also present in arteries, heart, kidney and intestine. This enzyme plays an essential role in lowering blood pressure. When blood pressure is high enough, it undergoes catalytic cleavage of angiotensin II, a vasoconstrictor into angiotensin, a vasodilator. Binding of SARS CoV 2 to these proteins causes a reduction of hACE2 on the cell surface, hence no control of blood pressure occurs which is one of the symptom of COVID-19.

According to research [8], virulence protein expression was studied by cDNA encoded with s (spike) protein and 3xFLAG tag, incorporated it into a lentiviral pseudovirion by the elimination of the last 19 amino acid sequences of the lentiviral genome. These virions were transfected with cell lines and expression was determined

by western blotting technique, virulence protein is detected by mouse anti-FLAG M2 antibody. Also it was reported that SARS CoV-2 s protein can also be rarely detected by rabbit polyclonal anti-SARS S1 antibody T62, these T62 antibody may include some non-conserved region of SARS CoV, 2013. Their research determined the possible targets of SARS CoV2, with a positive control VSV-G pseudovirion and the negative control of particle without any spikes. The entry of viruses determined by luciferase activity. Luciferase is the oxidoreductase that produces bioluminescence, used for many applications in the field of life sciences. It is used in genetic engineering to determine the reaction of interest. Hence, SARS CoV 2 transcriptional process can be detected after it enters the cell. They also proved that SARS CoV-2s mimics pseudovirions are used to transducer BHK cells, which stably expresses human amino Peptidase N (hAPN) which is the receptor of human CoV (SARS CoV-2) 229E, 293 cells expressing hACE2 protein detected by flow cytometry. By experimental prediction of various viral entry and virulence activity; They proved that SARS CoV-2 s pseudovirion which mimics the SARS CoV-2 s protein can be inhibited if the virus is preincubated with soluble hACE2 protein in an amount of 10microgram/ml or 50microgram/ml, act as a therapeutic inhibitor, which proved that the spike protein bind to the only hACE2, in preincubated for as its already bound then it doesn't show any harmful effect in trials.

According to the research, the endocytic entry of SARS CoV-2 pseudovirions by using either NH_4Cl or bafilomycin A (incubated with hACE2), these are the lysosomotropic agent, which help substances to pass into the lipid layer of the cell. Along with those, phosphoinositides play many important roles in endocytosis. The (PIKfyve) Phosphotidylinositol 3 Phosphate 5-kinase, is the major enzyme help in endosomal activity and endocytosis. They found that, YM201636 is the PIKfyve inhibitor; it was proved that treating the cells with YM201636 inhibits the fusion and reduces the entry of SARS CoV-2 s pseudovirions on 293/hACE2 cells, this drug is produced by InvivoGen. It also came to know that Cathepsin L act as protease and helps in cleaving the viral genome and express the virulence activity, along with that the major Type-II Membrane Serine Protease (TMPRSS) mediated cleavage can activate the fusion potential of SARS CoV-2 higher than CoV 1 and MERS CoV. No exogenous protease priming triggers the process of receptor binding or shows exponential virulence activity than the other two strains. They also SARS CoV-2 s protein is less stable and require shorter time and lower temperature for inactivation. They observed cross-neutralization activity by obtaining serum from recovered COVID-19 patients which moderately effective neutralization effect against SARS CoV-2 pseudovirion, which proves that convalescent serum from recovered one might not fully protect against newly infected ones.[8]

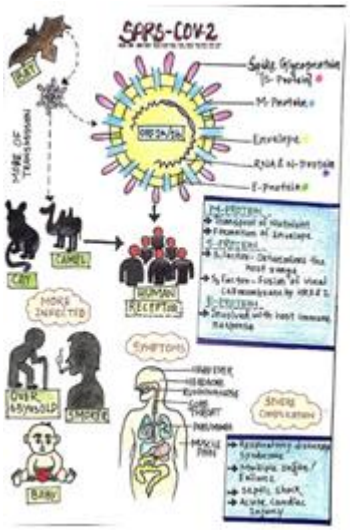

Fig 1:- SARS CoV-2 structure and its Virulence action

➢ *Proteolytic cleavage, increase virulence efficiency*

Ubiquitinyl hydrolase 1, the protease plays the main role of virulence and is, therefore, is an attractive target for drug discovery. It is a peptidase 30 type. This is the key enzyme for viral polyprotein processing. Along with this protein cysteine protease another main protease of SARS CoV, it has chymotrypsin like fold. This enzyme cleaves the translation product of the replicase gene of SARS. Hence, inhibition of the Mpro leads to the prevention of the proteolytic processing of replicase and minimizing the rate of production of infectious virus particles. According to PDB, these catalytic residue plays an important role in virulence activity, these residues are Cys145A, Gly143A, Cys145A, His4A; all these residues are from a single subunit A, which could be a matter of concern for research and development of therapeutics. Some of these residue act as electrostatic stabilization, nucleofuge, nucleophile, proton acceptor, proton donor, etc.

1st Preference (Optimal care for all hospitalized patients to decrease spread)	2nd Preference (Patients with other clinical complications and in high risk category)	3rd Preference (First responders and hospital workers health should be taken into consideration and also to avoid community transmission)
• Treating all patients with equal importance • Health workers with symptoms should be tested	• Patients above the age of 65 years • Patients with other clinical complications and underlying conditions should be treated with utmost care	• Critical infrastructure workers with symptoms • Individuals who do not meet above categories but have symptoms • First responders and health care workers without symptoms should be tested time to time

Table 1:- Criteria to guide evaluation and testing evaluation and laboratory testing for COVID-19. [10]

➢ *Some common symptoms :*

Shortness of breath, Mild increase in temperature, Continuous cough, Mental fatigue, Stomachache with frequent toilet visits, Feeling tired, Loss of taste/smell, increased blood pressure.

Fig 2:- Viral entry and it's mechanism of action

➢ *Serial interval, the transmission efficiency measurement*

A study by Hiroshi Nishiura et al 2020 on "Serial interval of novel corona virus/ COVID-19 infection" by observing 28 pairs of infectors and infectees. According to their study, COVID-19 infection leads to a rapid cycle of transmission of the median serial interval as 4 days to transmit from one generation to different. A serial number is an epidemiological study to estimate between successive cases in a transmission chain. The time between the infection and transmission, when gets shorter compared to the Severe Acute Respiratory Syndrome, which predicts the number of contacts may exceed than the handling capacity of available health care and public health worker. By Lie et al 2020, Linton et al 2020, the predicted median serial number is shorter than the estimated mean incubation period of 5 days. In this case, pre-symptomatic transmission occurs which likely to occur more frequently than symptomatic transmission. Also there is a chance of secondary transmission before the onset of symptoms and illness. [11]

Symptomatic Transmission	**Pre-symptomatic Transmission**	**Pre-symptomatic Transmission**
Infection symptoms Incubation period Serial Interval	Incubation period Serial Interval	Incubation period Serial Interval
Incubation period ≤ Serial Interval	Incubation period > Serial Interval Serial Interval > 0	Incubation period > Serial Interval Serial Interval ≤ 0

Table 2:- The connection between the hatching time frame and sequential interim. In the event that the transmission happens during the symptomatic time of the essential case, the sequential interim is longer than the hatching time frame. In any case, this relationship can be turned around when pre-symptomatic transmission happens. Besides, it is conceivable that the auxiliary case may even experience disease beginning before beginning in their infector.

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➢ *Transmission : The cause of pandemic:*

Corona virus contagion has been a matter of deep vexation, which is one of the top priorities in every country's government policy to stop its spread. Cross community spread of the virus among the population is what many of the people are concerned about how to save themselves from this brutal virus. The symptoms and transmission ways are well known all over the world. There are two main ways of transmission which have been described as following: The primary and foremost transmission method is direct contact of a diseased person with a healthy person. Another way by which it can also spread if the person infected with virus coughs or sneezes to discharge the respiratory droplets into the environment which is taken up by a healthy individual. Along with the person showing symptoms, there may be high risks of acquiring the virus from asymptomatic patients. According to John Hopkins Research Institute, it takes between two to fourteen days to show the symptoms for the corona virus. Rather than symptomatic transmission a greater danger is the cases that go undetected because of no symptoms and that is the reason asymptomatic transmission can be very much lethal, which will further add woes to the already rising number of positive cases. It may well be noted here that if in the meanwhile the asymptomatic cases are not identified it is no doubt that it will recur again in masses in population and this epidemic may never end. Leads towards a pandemic condition.

➢ *Anti-Pandemic strategies*

Till now, when the disease COVID-19, taken a shape of a pandemic, there were no therapies available only because of time which is required for now drug development. Hence, knowing the target site and targeting a similar therapeutics drug to this site is the only option like hydroxychloroquine, which is the anti-malarial drug that is the solution to some extent as it not directly preventing from SARS CoV-2 but speeding up the recovery. This is accomplished by target-based ligand screening by various computational methods. According to the research, there are around 21 targets screened which were screened against the compounds of Zinc database drugs. COVID-19, the disease by the not completely new virus but the virus with slight modification may be due to mutation from SARS CoV, became SARS CoV-2 cause human fatal pneumonia in patients along with Acute Respiratory Syndrome. [12]

The International Virus Classification Commission (ICTV) classified 2019nCoV as Severe Acute Respiratory Syndrome Corona virus 2 (SARS CoV-2) on February 11th, 2020 and WHO named the disease caused by this virus is COVID-19. Which have common symptoms like fever, cough, shortness of breath, dyspnea. In severe cases infection can cause pneumonia, kidney failure, even death. This virus has a positive viral RNA genome and also it belongs to β-genus of the coronaviridae family. It contains 4 proteins:

S- Spike, E-Envelope, M-Membrane, N-Nucleocapsid

Tough interferons act as innate immunity and stop spreading of the virus inside the body, but the infection takes place enough to show symptoms or with lower immunity individuals it can cause death.

3 strategy followed to fight against this pandemic:

1. Test existing broad-spectrum antivirals; which include α-interferons, ribavirin, cyclophilin, etc; Advantage: Metabolic characteristics, dosages, potential efficiency, few or no side effects; Dis-advantages: Too broad spectrum can't kill the virus in a targeted manner.
2. Using databases of known and existing molecules with few or some therapeutic role against corona virus. High-throughput screening makes the strategy possible also we can found the new function of different drugs.
3. Genomic information plays a significant role in knowing the viral mechanism and pathological characteristics to develop new targeted drugs, this is done by using PCRs, sequencing tools, immunoblotting and all.

Papain like Protease (PLpro)	**3C- like Main Protease (3CLpro)**	**RNA dependent RNA polymerase (RdRp)**
N- terminus of the replicase poly-protein to release NSP1, NSP2, NSP3. Essential for correcting virus replication. It is also confirmed to be significant to antagonize the host innate immunity. The most effective drug is ribavirin bind to PLpro at very low binding energy (-38.58 Kcal/mol).	3CLpro directly mediates the maturation of NSP, which is essential in the life cycle. Anti-asthmatic drugs (montelukast) also show low binding energy with 3CLpro.	NSP12 conserved protein. It is the vital enzyme for replication or transcription complex. Target inhibition of NSP12-RdRp couldn't cause significant toxicity and side effect is host cell, but no specific inhibitor is found till now.

Table 3:- One of the possible ways to stop this pandemic, it by preventing the viral RNA synthesis and replication inside the host cell. NSPs are involved in RNA transcription, translation, protein synthesis, processing modification. Among them 3Clpro, PLPro, RdRp are the most important targets for the development of small molecules of inhibitions. [12]

III. THERAPEUTICS AND RECOVERY

The newly evolved SARS CoV-2 from previously developed SARS CoV, 2003 and MERS CoV, 2012. The mortality rate is much high in (2019nCoV). Due to rapid spread, and the pandemic situation generated there is no vaccine or antiviral particular for CoV2. [13]

Ribavirin along with corticosteroids	Protease inhibitors	Immunomodulators	Host directed therapies
According to theoretical knowledge, this should have some effect on the virus. But not much efficient result obtained in-vitro, theoretical hypothesis is known but it is known for its side effects like hemolytic anemia, hypocalcemia, etc. Many shows to increase the viral load, so stops investigation. Lack of suitable control group in studies, preventing from getting a correct and efficient result for evidence.	Two types of protease found; CL-like protease and Papain like protease, which is the poly-protein and non-structural protein. (NSP 1-16), this cleavage carries most of the virulent function in the CoV lifecycle. Lopinavir, the most active inhibitor of these proteases and saquinavir is the least powerful one, can inhibit these proteases whose activity enhances the virulence property of the virus. According to Hong Kong University, the minimum concentration of lopinavir required is 4 microgram/ml. Ritonavir is added to lopinavir to increase the efficiency of the drug action and helps in fighting against SARS CoV-2.	Some benefits observed in $INF\alpha^{+}$ in high doses. Better results obtained when combinational use of corticosteroid and INF show less disease-associated oxygen impairment. Cytokines which increases in higher number after consuming the anti-malarial hydroxychloroquine is the only hope due to promising results in the fastest recovery	Metformin, Atorvastatin, etc helps in treating Acute Respiratory Distress Syndrome by increasing immunity. Zinc is a good inhibitor of RNA polymerase. Hence, hampers viral replication. Chloroquine increases the endosomal pH and thus makes the environment unfavorable for virus/ cell fusion also affects the glycosylation of Angiotensin-Converting Enzyme 2 receptor binding for viral spike protein; hence non-expensive, easily available and choose d as a promising candidate.

Table 4:- Different medium of therapeutic actions

➢ *The hope of recovery, by currently proved non-specific drugs*

As of now, when is there no way to treat the novel strain of corona virus SARS CoV-2 which had taken the shape of a pandemic condition COVID-19. Many scientists have tried many drugs just by keeping in mind the general virulence mechanism; enzymes, receptors, spike protein (s). None of these therapeutic approaches have been approved by the U.S. FDA. But based on treatment and occasional results, from few patients and clinical trials. These In-Vitro trials are our only hope for now. According to the WHO, CDC, U.S. FDA; there is neither medication nor vaccination proven effect against SARS CoV-2. This unapproved medication can cause an adverse effect, hence not recommended for young and healthy patients with few symptoms and no underlying comorbid conditions.

Chloroquine	**Hydroxychloroquine**	**Lopinavir, Ritonavir**	**Remdesivir**	**Fevipirevir**
• Antimalarial drug • Immunomodulating properties(Cytokine stimulation) **Mechanism** ▪ Inhibition of viral enzyme polymerase ▪ Viral protein glycosylation ▪ ACE2 spike protein, cellular receptor inhibition ▪ Avoid fusion to host cell **Effect** Cardiac arrhythmias Retinal damage Diabetes **Experience**	• Antimalarial drug • Immunomodulating properties(Cytokine stimulation) **Mechanism** ▪ Inhibition of viral enzyme polymerase ▪ Viral protein glycosylation ▪ ACE2 spike protein, cellular receptor inhibition ▪ Avoid fusion to host cell **Experience** More effective than chloroquine EC50 value 6.25µM at 24 hours and 5.85µM at 48	HIV protease inhibitor Invitro study is effective against SARS CoV-2, MERS CoV **Mechanism** Bird and black M pro which inhibit replication and supress corona activity **Experience** Mortality reduces to 19.2% than	Investigational nucleoside analogue Broad spectrum antiviral drug **Mechanism** ▪ Adenine analogue hence inhibitor RNA-dependent RNA-polymerase. ▪ It compete with normal adenosine triphosphate and as these don't have 3' OH group, chain termination occurs and stops RNA	Investigational RNA-dependent RNA-polymerase inhibitor Broad spectrum antiviral **Mechanism** ▪ RNA-dependent RNA-polymerase inhibitor ▪ Viral RNA synthesis ▪ Investigational intravenous drug with pre-mature termination of RNA transcription.

EC50 > 100µM at 24 hours and 18.01µM at 48 hours	hours Fever and cough recovery time decreases to 1 day early(~ 2 days rather than 3 days) **Effect** Cardiac arrhythmias Retinal damage Diabetes	25% Effect Cardiac arrhythmias Hepatitis	synthesis ▪ Drug appears to evade proof reading by viral exoribonuclease. **Effect** No adverse effect	

Table 5:- Possible options

➢ *Mechanism of passive immunization help in the prevention of COVID-19*

Their study demonstrates the potential immunotherapy with IVIg could be employed to neutralize COVID-19. Efficiency can be better if the immune IgG antibody specific to the particular target of the viral protein collected and transferred to non-immune one, can boost the immune response and the pathogen collected during the collection of plasma can be treated with detergent, 60℃, Anti-Viral Drug. [14]

➢ *Recovered patients help newly infected ones. COVID-19 Convalescent Plasma*

We all know plasma of the blood contains immune cells, antibodies with a wide diversity. Despite low efficiency and a long period of response to creating particular B cells (antibody-producing plasma cells) against spike proteins of SARS CoV-2 which bind to the ACE2 receptor in human cells, which is the normally acquired immunity of the body. Once these B cells developed and the person is cured. The antibody particular to the spike protein, which blocks the spike protein and interfering in the fusion of a virus into a cell; can be collected from the plasma of recovered patients is collected and purified. These can be transferred to the newly infected one in an extreme case, which is called passive immunization. This technique was the only option during many infectious diseases like swine flu, influenza, etc.

As many types of research going on to develop a vaccine, therapeutic solutions and potential of already available antivirals. This could be the only option to treat patients with severe or immediate conditions from life-threatening COVID-19 infections. This process may seem to be effective theoretically but it doesn't guarantee any prevention chances. Various clinical trials were made under traditional IND regulatory pathways.

➢ *Single Patient Emergency IND*

After several clinical trials, both invivo and invitro; U.S. FDA provides access to COVID-19 convalescent plasma for serious patients through a process of patient's physician requesting a single patient emergency Investigational New Drug (eIND) application. According to researchers, there is no 100% confirming result because of two reasons either there must be some allografting interference from person to person, due to which the antibody doesn't show the same result in all patients or the antibody present in plasma is already neutralized by spike proteins so there is no epitope available for binding with a virus after getting into the new patient. There must be some reason for insufficient antibody titer present in plasma to be capable of preventing fusion of the virus to a human cell in other patients to which it has been transferred.

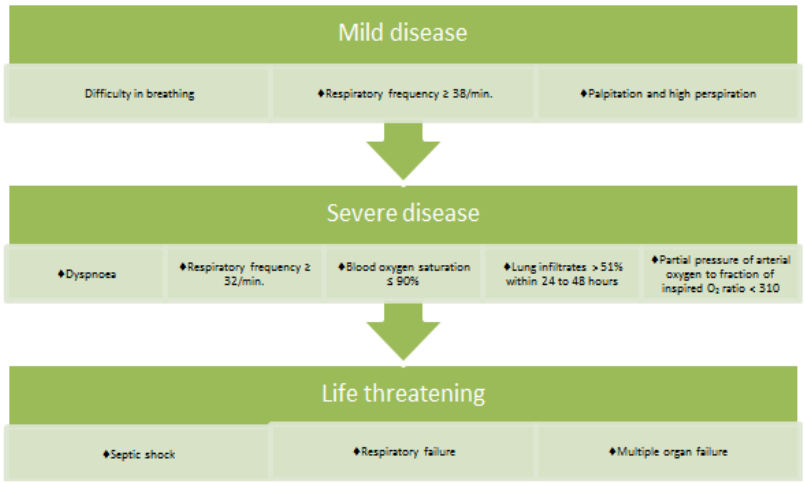

Table 6:- Criteria to access this plasma: According to CDC.

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➢ *Vaccine: The immunological approach*

Severe Acute Respiratory disease which is a highly infectious disease which was 1st seen in Guangdong province, China in November 2002. Many efforts to prevent this spread of the virus and the spread of virus stopped in 2003, with over 8000 positive cases and 800 death cases. There is a mindset that if this virus is being leaked by a terrorist group can lead to the pandemic condition, by the US Government. The protocol concerned, many testing occurred with phase 1 inactivated strain SARS CoV vaccine administrated both with or without adjuvant which is aluminum hydroxide (alum) adjuvant. The main purpose of developing a vaccine is to control in the event of an epidemic occurs or a widespread virus. One of the virulence mechanism is neutralizing antibody that binds to the receptor, ACE2. [15]

Two objectives: ;- 1st: To access reactogenicity of them both with or without adjuvant; 2nd: To access immune response to each vaccine, after a month with a single dose.

The mode of administration for this vaccine for many trials is intramuscular.

➢ *The new emergence of the vaccine mRNA based.*

A new RNA based drug that is being developed by Pfizer US and BioNTech Germany companies together. They have also given contributed to developing mRNA based vaccine for Influenza.[16] On 10th January, when the 1st phase of the SARS CoV-2 was detected and its genome was determined, within 42 days Moderna Therapeutics has developed an mRNA vaccine (mRNA-1273) which stops the spikes to fuse with the human cell surface. But there are many challenges, as a vaccine needs many clinical trials and approval which is taking too long for the pandemic situation, the company hoping to be available for universal immunization in about early 2021.

A new RNA based drug that is being developed by Pfizer US and BioNTech Germany companies together. They have also given contributed to developing mRNA based vaccine for Influenza.[P] However, it is turning out to be progressively certain that the most concerning issue for medication and immunization manufacturers, isn't which restorative therapeutics or vaccination stage to seek after. It is that ordinary clinical advancement ways are protracted and awkward to address the present general wellbeing danger. Several researchers are presently investigating, how to retool the improvement procedure to discover the possible options. [17]

➢ *Vaccine for Tb (BCG) could help in preventing COVID-19*

In the current investigation, when there is a wide reason for going down to fight against this pandemic. Some investigations looked on the effect of COVID-19 as far as the case fatality rate with countries with a high peak of the disease and the country with BCG revaccination policies, which provide added protection to the population against severe COVID-19. The Bacillus Calmette-Guérin (BCG) vaccine is a live attenuated strain derived from an isolate of Mycobacterium bovis and has been used widely across the world as a vaccine for tuberculosis. A live attenuated vaccine means that it uses a pathogen whose potency as a disease producer has been artificially disabled, but whose essential identifying characters, which help the body mount an immune response to it, have been left unchanged. [18]

Universal BCG which is the common vaccine for tuberculosis which shows similar symptoms and causes infection in airways and lungs, can also have a protective effect against COVID-19. Clinical trials of BCG vaccine are urgently needed to establish its beneficial role in COVID-19 as suggested by the epidemiological data especially in countries without a universal BCG vaccination policy. According to the data on experimental analysis of the observation by two studies by Miller et al and Hegarty PK. There was reduced mortality due to COVID-19 in countries with universal BCG vaccination policy.

Hence, universal BCG vaccination policy is observed with a reduced or lower mortality rate due to COVID-19 and also for low or middle-income economies. A national program of universal BCG vaccination appears to have a lower incidence and death rate from COVID-19. The protection offered by the BCG vaccine to SARS CoV-2 has been attributed to its non-specific effects (NSEs). The range of NSE includes of respiratory infection in children, anti-viral effects, reduced viremia. According to the study, low resources countries like India from the mid 20th century, the practice of BCG vaccination policy established. Unlike developed countries, where tuberculosis rates are declined. Hence, considered a target BCG vaccination for high-risk population, have considered practicing BCG vaccination policy to decrease the mortality rate by COVID-19 by lowering the symptoms, which is a great hope to slowly fight against this pandemic until the proper vaccine have been developed. [19]

➢ *Drugs and Vaccines in research around the World*

A leading global biotech company has released its 1st batch of vaccine against novel corona virus used in February 24 which has officially been named "mRNA-1273" vaccine which is shipped for its phase-1 study to NIAID (National Institute Of allergy and infectious disease) in USA. This vaccine will go through a clinical test by 45 volunteers to ensure its effect against COVID-19 in a research centre of Seattle.

USA: It is known that Remedesivir an antiviral drug produced by the US-based pharmaceutical company Gilead Sciences is tested against Covid-19 among all the 293 drugs taken for trials. It has been applied against covid at the beginning of last month. England Journal of medicine has published in accordance with the statement given by assistant director general of WHO- Bruce Aylward. The US Food and Drug administration (USFDA) approved *chloroquine* and *hydroxychloroquine* as a treatment of Covid-19, which is already used to treat malaria and arthritis.

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China: *Favilavir*, an anti-viral drug which is approved by National medical product administration of China for the treatment of Corona virus. In Schenzen, Guagdong province a clinical trial is done with 70 patients. It shows efficiency in treating disease with minimal side effects.

Pharma Companies	**Drugs/Vaccines**	**Effect**
Entos Pharmaceuticals	Fusogenix DNA vaccine	Not proved
Oxford University's Jenner Institute	chAdox nCov-19	Adenovirus vaccine vector
Roivant Science	Gimsilumb	It will attack GM-CSF (Granulocyte macrophage colony stimulating factor) which is found in serum of Covid-19 patient. This drug will help to reduce the lungs damage.
University of Albama at Birmingham and Altimmune	Adcovid (Single dose intranasal vaccine)	Similar to NaSovax, an influenza vaccine
I-Mab Biopharma	TJM 2 (Neutralizing Ab)	It will target GM-CSF responsible for acute and chronic inflammation in corona patient
Medicago	Drug candidate against Covid-19	It is collaborated with Laval University research centre to produce Ab against SARS-Cov-2
Airway therapeutics	AT-100 (Human recombinant protein)	It will reduce inflammation and infection in the lungs, to increase immune response against disease.
Tiziana Life Science	TZLS-501 (Monoclonal Ab)	It is a human anti-interleukin 6-receptor (IL-6R) The drug will bind to IL-6R and reduce the amount of IL-6 and lung inflammation.
Oyagen	OYA1	In comparison with chlorpromazine Hcl, OYA1 will be more effective in inhibiting SARS-Cov-2.
Algernon pharmaceuticals	NP-120	The clinical trial will test the effect of drug
Inovio and Genome Life Sciences	INO-4700 (GLS-5300)	High immune responses against MERS-Cov
Roche	Actemra	Prevents cytokines storms and over reaction of immune system
Biocryst Pharma	Galidesivir	It is a nucleoside RNA polymerase inhibitor that stops the process of viral replication
Regeneron	REGN3048 & REGN3051	
Lattice Biologics	AmnioBoost	For treatment of acute respiratory distress syndrome (ARDS) in Covid-19 patient

Table 7:- A number of drugs are developed and tested for the treatment of the novel corona virus by pharmaceutical companies and research organization =>

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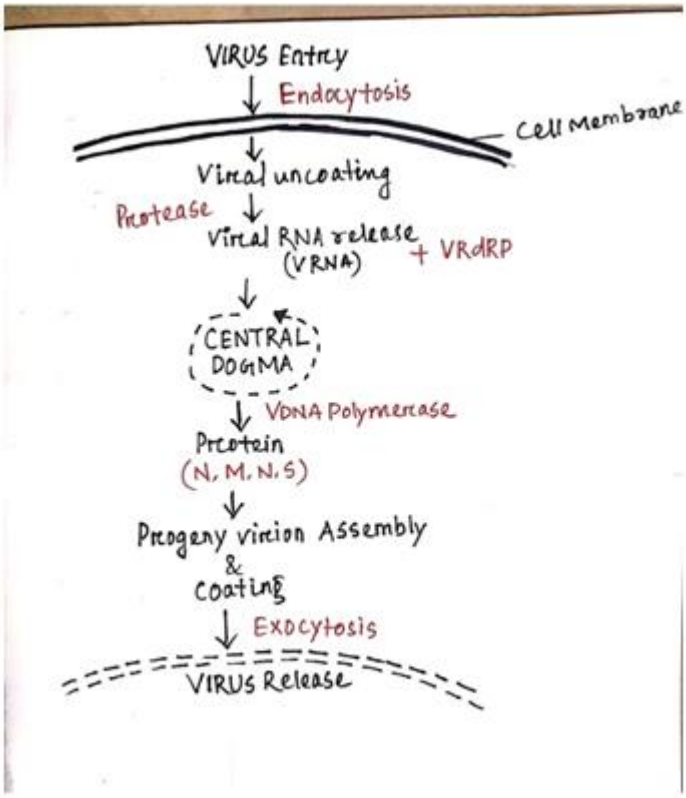

Fig 3:- General process of viral entry
{Source- (D) Coronavirus treatment: Vaccines/drugs in the pipeline for COVID-19}

IV. WHY LOCKDOWN IS SO IMPORTANT?

Is SOAP the ONLY DRUG? The outer coat of the SARS CoV-2 is a lipid (fatty) bilayer (called envelope). Soap helps in dissolving the fat membrane, hence virus will leak out and dye. Virus is a lipid sac containing RNA genome inside and protein spikes projecting outward. This virus is of size 50-200 nm hence nanoparticle size, the genetic material easily injected into the cell with the help of spikes on the viral surface. The RNA genome in the call after getting into the cell self replicates and hijacks the system machinery of protein synthesis, according to the information present in RNA genome called translation. These proteins assemble and form many copies of viruses that burst out of cells and infect other cells. These viruses end up in airways by mucous membranes.

CROWDING means SPREADING: As we know the virus mainly infects airways and lungs, so when we sneeze tiny droplets may or may not virus can fly maximum up to 10 meters (30ft)and the virus comes in contact with the skin of uninfected ones or taken up into airways as a person breathes in. According to the study, the powerful supramolecular chemistry says that a similar molecule appears more strongly that dissimilar one. On fabrics or wooden surfaces, it forms hydrogen bonding and is less stable than steel or Teflon, so it's recommended to not touch these dirty surface, clean hand from time to time. Moisture, sunlight, heat all makes the virus unstable.

Why should you not TOUCH your mouth/nose/eyes without washing? The skin is a perfect surface for infection by virus or any other microbe and the proteins and unsaturated fats in the dead cells on the skin, cooperate with the infective organism through both hydrogen bonding and hydrophilic attraction. So when you contact says a steel surface with an infection molecule on it, it will adhere to your skin and consequently get moved onto your hands. Yet, you are not (yet) tainted. If you contact your face however, the infection can get moved from your hands and on to your face. What's more, presently the infection is hazardously near the aviation routes and the bodily fluid sort layers in and around your mouth and eyes.

Soap: destroyer of viruses: Normal it is ok, but not as efficient as soap water. fat-like substances present in soap known as amphiphiles, which mimics the lipid of the virus's outer membrane. Hence, interact with the viral membrane and also we know detergents like SDS break the bonds in protein and change the conformation and function of the protein. [20]

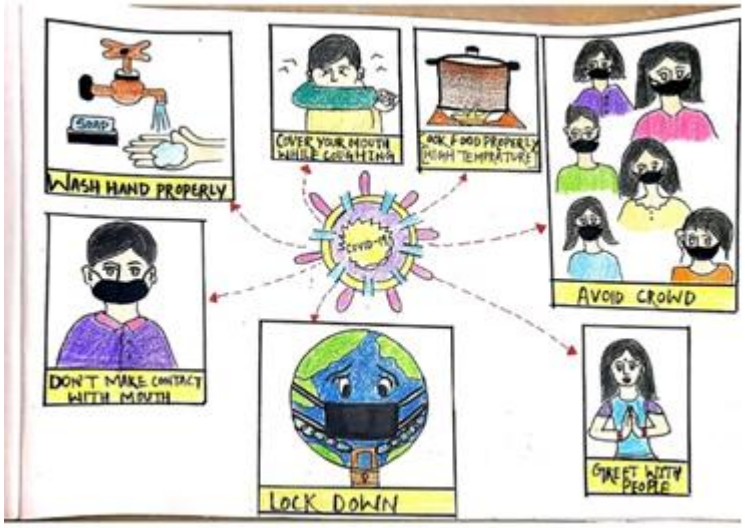

Fig 4:- Social responsibility to avoid this contagiousness

➢ *Influence of temperature, pH on CoV 2019*

An increase of 1° C and 1% relative humidity lowers the transmission of viruses according to some data. Korea, Japan and Iran with relatively lower air temperature and lower humidity and had a severe transmission of Corona virus. According to Accuweather founder and CEO Dr. Joel L Myers, in cold and dry condition virus survives for a longer period, but in the warmer condition it is less lethal and less effective on humans.[2] It does not mean there is no transmission. It is hard for corona virus to survive in the air/ on surfaces for a long period atawarmer temperature. The researchers found that transmission of coronavirusmostly occurred at low temperatures between 37.4 and 62.6 F(3-17° C).There have been different reports on indirect relation that shows links of lesser cases of Corona virus in tropical countries. According to the research of Jingyuan et al. on relative humidity and temperature they have established and proved a direct relation to COVID-19 cases where high temperature and high relative humidity significantly helps to reduce the transmission of COVID-19. [G] They have also proposed two intellects regarding it where the first reason was that the virus strain is stable at low temperatures, so the droplets as carriers of the virus remain suspended in dry air for a longer period. The other reason which they tried to justify was that a hosts' immunity gets compromised due to dry and cold weather which in turn makes the body easily predisposed for the virus to attack. [7] Corona virus grows at a favorable pH of 5.5 -8. Change in this environment for the virus makes them unstable and it dies.[6] Evidence of pH influence can be deduced from the fact that the much-hyped savior drug as of now *chloroquine*and some other FDA approved drugs as azithromycin and ciprofloxacin work by pH alteration in the respiratory epithelial cells. These drugs are all weak base hydrophobic which helps in neutralization and anisotropic effect, which in turn acts on the spike of CoV2 spike cleavage to block its entry into the respiratory cellular system.[F] From this we can infer that pH also has some influence in COVID-19 virus transmission.

➢ *New Concept about the virulence action of CoV*

A new theory is coming up for lungs involvement in COVID-19, as it also has hACE2 protein on its cells and supporting lungs toxicity is due to oxidative depletion of hemoglobin and methemoglobin releasing porphyrin and free irons. The doctor noticed that the ventilators are increasing COVID 19 related deaths by inducing hypoxia which results in oxygen activation to free radicals. Doctors also noticed little or no pneumonia in patients. This mechanism is based on observation in the USA, Spain, Italy. Most of the post-mortem revealed pulmonary thrombosis not typical ARDS. Like methemoglobin, the viral structural protein stick to heme displaces oxygen and irons. Hence, free iron toxicity causes inflammation. So, no need for ventilation, only frequent transfusion of blood is essential. The heme has 4 subunits two of which are α-subunits and the other two are β-subunits. The virus attack on the β-subunit, dissociates heme, removing iron and converting to porphyrin, hence porphyrin can attack oxy-Hemoglobin, carboxy-hemoglobin and also glycolylated-hemoglobin. According to this new concept, Chloroquine can compete with virus binding to porphyrin. Favipiravir binds to the virus envelope protein with high affinity, prevents entry into the cell as well as binding of a structural protein to porphyrin.

V. DISCUSSION

The new infection, which cause the pandemic situation all over the world COVID-19, caused by evolved strain of CoV, which is SARS CoV-2, 2019 from previous strains SARS CoV, 2002 and MERS CoV, 2012. All these infect human can cause Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome, to which result into pneumonia and cause death. According to the research and studies, may be theoretically or experimentally; it has been proved that hACE2 could be the only and most important binding site for viral spike protein, for fusion with the host cell. So, as hACE2 have a major role of controlling blood pressure the viral inactivation of hACE2 protein found on the cell surface of lungs cell,

increases heart rate. This is proved by researchers by making a CoV2 like virus by use of a lentivirus and incorporation of a viral protein into it, which shows same corona like activity, which is validated by taking positive and negative controls. Also, many experimental practices proved YM201636, the PIKfyve inhibitor as PIKfyve plays a major role in endocytosis of virus genome into host cell, this drug blocks endocytosis and stop viral further replication cell division, and control viral spread. The viral protein undergoes a proteolytic cleavage after incorporating into a cell by enzyme called Type II Membrane Serine protease and along with that host cell protease ubiquitin hydroxylase l and cysteine protease; cleaves the translated product and lead to virulence activity. Serial number is a unique study of understanding the transmission possibility and efficiency in a theoretical manner. As the incubation time of a virus is 12-14 days, it is matter of concern to underestimate the asymptomatic condition, virus become dormant to get rid of the unfavourable condition. When the favourable condition comes, it again became virulent like bacteriophage does in lysogenic pathway, to bacterial cells.

The genomic make up, makes this nanoparticle size organism very much intelligent, which make itself dormant by consumption of non-specific anti-virals. These antivirals or well-known hydroxychloroquine change in environmental which makes it unfavorable for virus. That's may be the reason of reoccurance of symptoms, according to recent observation. The 3 strategy of fight against this pandemic by use of common broad spectrum, known bioinformatically proved and genomic data and PCR. Based on clinical trials and unexpected hope of drug estimation results of hydroxychloroquine, which inhibit the hACE 2 temporarily to avoid the binding spike S protein and phenotypically it observed by rapid recovery from fever and increases the rate of recovery, may be it don't have direct effect on virus, but it make the environment for harsh for virus to survive and multiply. Remdsivir is also proved to meet the therapeutic expectation. Vaccination is the, field where more importance is given as the only solution to eradicate this virus in future, as we know vaccine a small non-virulence part of virus for which activate immune response (IgG,IgM). As choosing a part from virus as a thing for increasing immunity leads to its wide spread takes it a very long time to manufacture. Company like Pfizer and Moderna Therapeutic works on mRNA vaccine, which is the part of genome build by cDNA, which after entering our system, codes for protein, by translation and the immune cell act against it can vaccinize the person without any side-effect. This based on genome analysis and genetic engineering method, by the use of Whole Genome Sequencing tools and PCRs. Which takes much time for analysis and its discovery will surely helpful for mankind. Tuberculosis vaccine (BCG), proved to be the major cause of controlled picture of pandemic in south asian countries like India but not in western countries where targeted BCG vaccine use is very limited and rarely used. Hence, western countries have high mortality rate than South-Asian countries.

Passive immunization proved to be a therapeutic as anti-CoV which is recovered from previously infected person and transferred to the newly infected one. WHO recommends its use in severe cases.Instead of all these trails for recovery and contamination blocking, the major thing is privative measures, as we mentioned in our review by various health care expert, the only medicine as of now is LOCKDOWN. According to the new concept mentioned in the review, there are few cases under careful observation, as fatigue is a symptom often seen in hypoxia, when less oxygen is passed into the body. Lack of oxygen makes human weak and person takes long breath, which is a matter of suffocation, which could be due to porphyrin formation and oxidative depletion of hemoglobin.

VI. CONCLUSION

The Earth has no doubt become a global village with the advancement of technology, but it can also be seen as a means which helped in spreading the disease more rapidly due to easy access of cross continental travel. The table has now turned against us where we are now caged in our houses fearing from a mere invisible particle which has totally taken the whole world under its control. It is high time to stop the political blame game, as done by different countries and focus more on its eradication. Rather than panicking it is time to collectively fight against it on a personal level by taking hygienic measures and practicing social distancing. Think much more considerably, otherwise sadly the next person on the number of cases list might be you.

"On behalf of all the authors, I would say there is no conflict of interest for this review paper"

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