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THE NOVEL CORONA VIRUS (nCoV2) SEEMS TO DEFY ALL LAWS OF VIROLOGY

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ABSTRACT: Amongst the known coronaviruses, many were responsible for causing disease in humans knowingly from the common cold to acute severe respiratory syndrome. The novel coronavirus, nCoV-2 has been implied to cause increasingly severe damage to public health besides demolishing the global economy with a staggering figure of continuous rise in mortality within the afflicted cases in almost every country on this planet. Owing to the perplexed scenario there are growing challenges involved in the containment of the spread of this novel coronavirus, which is mounting to be numerous and continuous. The battle is still on with this nCoV-2 since it has evolved, presenting with initial flu symptoms in patients affected to atypical pneumonia mimicking a catastrophic disseminated intravascular coagulation stage leading to cardio-respiratory abnormalities thus assuming proportions of mysterious illness to very unusual symptoms encountered in different age groups. The genomic analysis of the nCoV-2 has revealed constant potential mutations with the evolution of different strains, thereby posing numerous challenges to develop an effective vaccine that will hold a promise on providing long term immunity to the host. This review critically analyzes its arrival and spread across the globe to almost entire virology of this novel coronavirus to challenges that might be encountered in the future even if the vaccine is ready to combat the virus.

INTRODUCTION: Coronaviruses that affect humans were discovered in mid-1960s [1]. SARS-CoV-2 presently assigned as (COVID 19) is a 7th amongst known coronaviruses that cause infection in people, after 229E and OC43 (earliest studied viruses in human patients suffering from a common cold) [2]. Historically, the other "coronaviruses" were identified as the "SARS CoV-2003", HCoV with "NL63 in 2004, HKU1 in 2005", very recently, MERS- CoV in the year 2012. Most of these viruses produce clinically severe respiratory tract illness [3, 4].

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The infected patients with COVID-19 often experience common cold-like symptoms along with raised temperature, non-productive coughing, and difficulty to breathe [5]. However, the infection often leads to a state of pneumonia, failure of multiple organs, severe sudden respiratory distress that may often be fatal [6]. The aged and those with underlying chronic health problems have been known to account for a significant portion of deaths from "COVID-19" [7].

The novel coronavirus has brought the biggest humanitarian crisis to the world since the Influenza pandemic in 1918, which caused around 50 million deaths [8]. It is thought to be originated with a patient belonging to a Shrimp seller in the Huanan wet Seafood wholesale market in Jianghan district in central Wuhan of Hubei province in China [9]. To date (as on 15th April 2020), the novel coronavirus presently assigned as "the severe acute respiratory syndrome (SARS CoV-2)" has been accountable for over 2 million infections worldwide and causing impeccable 1,28,830 deaths. The virulence and lethality of COVID 19 is compounded by the fact that symptoms take at least several days to emerge; thus impact of this insidious virus which has spread across the globe cannot be chased for its affliction and eventually – has stemmed the tide [10]. The ongoing massive infection burst with this novel coronavirus has caused worldwide apprehension and distress as it is spreading extensively far and fast, thus causing dramatic deterioration to the people's health and global economy! [11]

COVID-19 also resembles the same illness as affected by SARS-2003 virus [12]. The first infection was unofficially reported from Wuhan city of China [13] have occurred on 17th November 2019. However, the official reported infection with first symptoms came from 4 workers within the same region of seafood wholesale market on 8th December, 2019.[14] The mysterious illness was thought to have evolved from animals which had caused mutations in the virus to affect the humans and related with animal coronaviruses like SARS (2003) and the mortality rate was up to 10% for SARS CoV and up to 37% for MERS CoV [11, 15]. It has turned out to be deadliest amongst the known coronaviruses affecting global population so far! [16]

The COVID-19 virus appears to be fiercely infectious, dreadful as it is making the countries across the globe to count daily new infections and deaths and push the tolls. This article reviews the entire virology of this novel coronavirus SARS-CoV-2; including its origin and arrival after mutation, how it is different from other coronaviruses, the possible mechanism of making their ways into the human cells along with other potential characteristics and possible ways which perhaps would help the research workers to develop the long term effective vaccine against COVID-19.

Tracking the "nCoV (SARS-CoV-2)":

(Origin of COVID-19 Pandemic: How the Pandemic has Spread?): The COVID-19 outbreak came without warning and spread like wildfire across the world by building a chain and clusters of transmission at different geographic locations. The outbreak of COVID-19 within no time spread across the entire Hubei province, many adjacent provinces. On December 31st of 2019, the WHO China county office reported and alerted of affected persons with "atypical pneumonia" of non-traceable cause detected in the city Wuhan, China [17].

On January 7th, 2020, Chinese health care workers identified a fresh strain of coronavirus responsible for causing the disease (SARS-CoV-2), having 79% of genetic similarity with SARS-CoV [18]. The epidemiologists suggested that it was less lethal but far more contagious (3to 4 persons were affected in the first stage of the spread) [19]. The persons then remained asymptomatic carriers in the first half of the illness, which lasted for 2 to 7 days have a lower infection rate. However, the second half of the illness was more severe than could infect via person to person spread [20]. That is why there was an unprecedented rise in the spade of infected cases as a substantial number of ordinary people feared to move away from the epicenter (reservoir) [21].

On 9th January 2020, a 61 year man died of this mysterious illness suggesting the deadly potential of this novel coronavirus [22]. On January 11, 2020 cases soared, and most of the provinces in China and adjacent countries like Hong- Kong, Singapore, Macau, Taiwan, South Korea, Japan began to show a rise of new cases. Thus the authorities confirmed through tracing the patients for human-to-human transmission being evident [23].

On January 21, 2020 WHO realized the worsening scenario mounting various challenges and came up with the first situation report as the authentic guidelines for handling the global spread of disease, which is then daily updated presenting solutions to the challenges arising out of the deadly spread of the disease [24]. On January 29, 2020 WHO declaration considered this novel coronavirus outburst as "Public Health Emergency of International Concern (PHEIC)", when it spread to affect other 31 provinces and 25 countries. On March 11, WHO declares this viral outbreak as pandemic [25].

Transmission of nCoV-2: During the SARS-CoV outbreak in western Africa, the emerging and re-emerging dynamics of the spread of the disease could not be timely declared by the authorities for human transmission. The official update of the outbreak was 4 months late to see the unprecedented rise in the cases [26]. In the case of "SARS-CoV-2" the official update regarding the dynamics of the infection underlining human-to-human transmission came one month late. The growing fear and anxiety of catching this killer virus suggest the population being ostracized [27].

Up to 10% of the COVID-19 patients leaving medical facilities are re-infected subsequently. The COVID-19 may be reactivating in individuals who have been cured of the viral disease (Korea's CDCP). Thus COVID-19 seems to defy the laws of virology showing numerous potential cases of "reinfection," which have left the Scientists perplexed! These instances would seem to suggest that COVID-19 operates differently from its predecessors SARS and MERS-CoV [28]. These two viruses never infected the same person twice. Needless to say, it is bound to pose a major health challenge under vaccine protection. Enhanced understanding of the immune system suggests that repeated infection may be the cause of mutations of the virus even at a smaller scale [29].

The original traceable source of viral transmission remained seemingly unclear, with doubts being raised if the strain turned pathogenic that might have occurred before or after the spillover event. Because many of the first patients infected by the virus were labors at the Wuhan wet sea-food market in Central Wuhan of China. It was speculated that the strain must have been evolved from the same market [30].

Transmission Facts of COVID-19: The perplexing and furious human to human transmission queries have been answered by WHO that "researchers are still studying the exact parameters of human to human transmission" [11]. Transmission primarily occurs *via* the spread of droplets in the air during respiratory bursts, coughing, and sneezing within the distance of about 1.8 meters (6Ft) [31] or even more distance (up to 13 feet) [32] when the level of infection is high. The contaminated surfaces serve as a source of indirect contact, which becomes another possible reason for infection. The virus persists sustainable on the surface of plastic and steel for about 3 days but does not remain viable on the surface of the cardboard for more than a single day or on copper for greater than 4 hours [33]. This transmission is called as fomite mediated transmission. Till the time viruses do not enter the human body, they are not even technically alive. They can remain in that state for eternity [34].

Inactivation of the virus can be achieved by lather, which destabilizes its "lipid layer". RNA of the virus is also encountered in samples from the feces of infected people, which again becomes another factor responsible for the spread of the virus [35]. However, the recent findings suggest that this virus is highly transmissible in humans defying the traditional parameters of the nosocomial route of transmission through air droplets and particles. The WHO consultant reiterated that individuals with the mild infection do shed the virus, and individuals with a severe infection also shed the virus. It can be learned that more severe the symptoms the individual has the more likely that he is going to transmit the virus [36].

Dr. Anthony Fauci, Director, "NIAID (National Institute of Allergy and Infectious Diseases)" confirmed from the data obtained by Chinese Specialists that the viral incubation period is probably between five to six days required for symptoms to arise once it has caused infection in a patient [11, 37]. On February 1, 2020, WHO declaration said that transmission from the cases which are asymptomatic is not likely to be a significant carter of transmission. However, based on model of epidemiology, in the start of the spread in China emphasized that pre-symptomatic detaching may be more distinctive amid confirmed and the sub-clinical infections that might have been the basis of a major portion of infections [38].

There is slight proof of communication of "SARS-CoV-2" from humans to animals, including few in felids and tigers and even stray dogs [39]. Although WHO indicate that estimation of the incubation period of this virus which experts estimate, may last somewhere between 1 to 14 days, they also suggest that the most likely duration period is 5 days [11, 40]. Research has indicated that peak viral load that reaches the pharynx takes approximately 4 days after the infection has occurred [11, 40, 41].

Data gathered from the epidemiological studies indicate that a piece of infection terminates in 1.4 to 3.9 fresh ones which is regarded as basic reproduction number (R_o: R naught) [42] of the virus, in a situation when no fellows of the community show natural resistance and no actions for prevention are taken [42, 43]. The R naught for COVID-19 is 3. Before a cell dies, it can churn millions of copies of the virus [44]. Professor Hugh Montgomery, Director, IHHP "(Institute for Human Health and Performance)" has illustrated that 10 infected people can pass on the novel coronavirus to 59,000 people [45].

The number of reproduction of the virus may be more in thickly inhabited scenarios such as those encountered on Voyage ships [46]. It was assessed that the rate of infection in the working class in and around Barcelona, Spain was nearly seven times higher than the upmarket areas. Moreover, in the Lombardy region of North Italy, the rate of infection was exuberantly higher than in Spain [47].

Why are Men more Susceptible to COVID-19 Infections than Females? Dr. Philip Goulder, a Professor in Immunology at Oxford University, analyzed the data of 14,860 COVID-19 infected patients and found that amongst them, 68% of males were infected. He stated that a number of factors impart women with more competent immune systems, including females having 2 X chromosomes to 1 in male counterparts, and that a significant number of critical immune genes are found on X chromosomes [48].

"In particular, the proteins by which viruses such as CoV are sensed are encoded on X chromosomes." That means the proteins are expressed double the dose on many immune cells in women when compared to men, which in turn could be strengthening female's ability to shield off COVID-19. Besides, more prevalent habits of smoking, drinking, obesity, and other unhealthy behavioral factors pose the eventual biologic risk for getting the viral infection in men [47, 48, 49].

German virologists say people initiate immune response after coronavirus infection by production of antibodies, and moreover, German Scientists are planning mass study to track immunity to COVID-19, as stated by Melanie Brinkmann from CIC and Friedmann Weber from Institute of Virology at the University of Gieben. According to Berlin Virologist Christian Dosten, it takes about 10 days for antibodies to form after a person is infected with nCoV regardless of mild, severe, or completely un-noticed infection. Someone with SARSCOV-2 is protected from renewed infection for at least few years. It is extremely unusual if antibodies produced against nCoV-2 did not protect them from renewed infection [50].

Fallacies around the Novel Corona Virus SARS-CoV-2: The virus cannot survive in variable weather conditions!

Seven conspiracy theories have been raised around the origin and spread of virus, *e.g.* bioweapon, 5G connection, escape from the laboratory, prediction in a 1981 novel "The eyes of Darkness" by Dean Koritzerrily predicts coronavirus outcome but none are substantiated [51].

A sequence of genome from "SARS-CoV-2" and allied viruses, which is made public by different research workers, found no evidence on analysis of data that the virus was constructed in the research laboratory or else engineered. Investigation findings have shown that the COVID-19 pandemic has a natural origin! [51, 52]

The Novel Corona Virus" SARS-CoV-2": "SARS-CoV-2" is one of the known "coronavirus" that cause "coronavirus disease 2019" (COVID19) [11]. Family of coronaviruses generally aim and afflict animals' pulmonary systems [53]. With regards to their typical features, there are four distinct genera of coronaviruses, which are known as "alpha, beta, delta, and gamma". Nearly most of these are known to effects animals only, but some of them can also manifest in humans. Amongst these viruses recognized to be transmissible to persons are related with only alpha and beta genera [11, 54].

Amongst the known, only two coronaviruses have caused a worldwide outbreak in the past. The preliminary of these was "SARS coronavirus" – accountable for a spread in China, Singapore, and Hong Kong, which ultimately waived off in the year 2003. The additional virus was "MERS (Middle East Respiratory Syndrome)" that originated in the Kingdom of Saudi Arabia in 2012 and had caused fatal illness in at least 2494 persons since then [10, 11, 55].

Origin of the Novel Coronavirus: Infection with coronavirus that arises in humans, typically occurs through interaction with an infectious mammal. Amongst them, the maximum conjoint carters are bats, although it is known that they do not stereotypically transfer the "coronaviruses" more openly to humans. Despite this, the spread might occur through an intermediate source, which regularly though not always is a native one [11, 46, 56].

The "SARS coronavirus" transmits to humans through "civet cats", while "MERS virus" spread by dromedaries (camel). However, it may be hard to trace the mammal from which the coronavirus primarily begin spreading [11, 57].

In the present scenario of novel coronavirus, preliminary reports linked the spread from a wet market in Central Wuhan. However, the later assessment has unfolded the fact that it was unlikely that this market was a single source or reservoir for the origin of outbreak [11, 58].

More recently, Chinese researchers in their study revealed that Sunda Pangolins may be accountable for the initial propagation of "SARS-CoV-2". On February 7th, 2020 it was stated that research workers from Guangzhou, China had traced its genomic sequence appeared to have a viral nucleic acid sequence to be 99% similar to that of coronavirus related to these animals. When declared, the results were substantiated considering the fact that the hooking up of S-protein to the receptor was almost nearly similar with just one amino acid difference. These serve as an intermediate animal reservoir, which is also thought for its introduction to humans. The minimal genetic diversity shown by this virus is suggested the spillover event, which is most likely to have occurred in late 2019 [59].

Peeping into the likely repositories of these virus strains, by researchers that produced the SARS 2002-2004 spread has culminated into the detection of many SARS similar bat coronaviruses, utmost of them instigating in the "rhinolophus genus" of horseshoe bats as well as the two sequences of the nucleic acid of the virus encountered in the samples taken from "Rhinolophussinicus" showed characteristics with 80% similarity to "SARS-CoV -2" [60]. The primary identified infections after the "SARS-CoV-2" strain had been found in Wuhan, China.

A third nucleic acid sequence of the virus taken from "Rhinolophusaffinis", encountered in Yunnan region and assigned as "RaTG13" has 96% proximity to SARS-2. The virus genome has a novel lineage for almost half of its genome, with no close genetic relationships to is close subgenus, sarbecovirus [60].

Etymology: The term "coronavirus" is taken from Latin word "corona", denoting "crown" or "wreath" simultaneously derived after the Greek "karone" or "garland wreath". The terminology denotes the typical emergence of virions (signifying the pathogenic type of virus) using electron microscopy (both SEM and TEM), which have tassels or twists of huge round surface projections generating a picture reminding of the crown of solar-corona. This characteristic figure is produced by viral spikes known as "peplomers", are the proteins present on surface of virus [61, 62].

How does the Novel Virus Compare with other Viruses? The Chinese researchers using the position of art genome in sequence of tools identifying the structure of DNA of the new CoV. It was learnt that "SARS-CoV-2" is almost identical to other two " coronaviruses" seen in bats assigned as bat "–SL- CoVZC45" and "–SL-CoVZXC21-" as the order of its genome with 88% similarity as theirs. The above-mentioned research has shown that DNA of this new virus is approximately 79% identical to that of "SARS coronavirus" and up to 50% the same as the "MERS virus" [11, 63].

In Texas, the geneticists and microbiologists have individually encountered data of re-assortment in coronavirus implicating the association of pangolins in the outbreak of "SARS-CoV-2". Moreover, the "pangolin coronaviruses" encountered to date only show at the most 92% of their complete genomes with "SARS-CoV-2" which make them substantially less identical than "RaTG13" to "SARS-CoV-2". Thus it becomes insufficient proof that pangolins be considered as an intermediate source. In comparison, the SARS virus known for 2002-2004 spread shared 99.8% of its genomic sequence with novel coronavirus [64].

The virus principally crosses human cells by adhering it to the ACE-2 (angiotensin-converting enzyme 2) receptor [11].

Structural Biology: The virion of each SARS-COV-2 is up to 50-200 nanometers in diameter [65]. Similar to another coronavirus, "SARS-CoV-2" also has 4 distinct morphological proteins, called as the "S (Spike), E (Envelope), M (Membrane), and N (Nucleocapsid)" proteins; the N-protein has RNA-genome, and together the S, E and M proteins build the cover of the virus [66]. The spike protein observed under the ultrastructural level with cryogenic electron microscopy, [67] is the protein that facilitates the adherence of virus to and mingles with the cell membrane of host [68, 69].

The experimental models of the s- protein of the virus readily revealed that "SARS-CoV-2" has enormous kinship for the ACE2 receptor on cells of humans to utilize them as portal of cell entry [70]. By Jan 22nd, 2020, a number of researchers in China operational with the complete viral genome and an assembly in the USA utilizing "reverse genetics" methodology self-reliantly showed that ACE2 could also act as the receptor for "SARS-CoV-2" [71, 72].

Research has demonstrated that the coronavirus displays twenty times higher kinship to human ACE2 compared to the new strain. Thus this new strain appears to be more readily transferred amongst humans. "SARS-CoV-2" may also utilize basigin, the extracellular matrix protein to help in cell entry [73].

Priming of original S-protein by "transmembrane protease", "serine 2(TMPRSS2)" is required for access of "SARS-CoV-2". Subsequently, a "SARS-CoV-2" virion adheres to the objective cell, the "TMPRSS2" nicks the S-protein of the virus, thus revealing a union of the peptide. The virion then discharges the RNA into the cell, compelling the cell to manufacture more copies of virus that are dispersed to transfect more cells. "SARS-CoV-2" produces a minimum of three virulence factors that allow detachment of newly formed virions from the host cells and also suppress "immune response" [68]. It is linguistically called coronavirus and prior stated by its supplemental name "2019 novel coronavirus (nCoV)". "SARS-CoV-2" is positive sense single -stranded RNA virus [69].

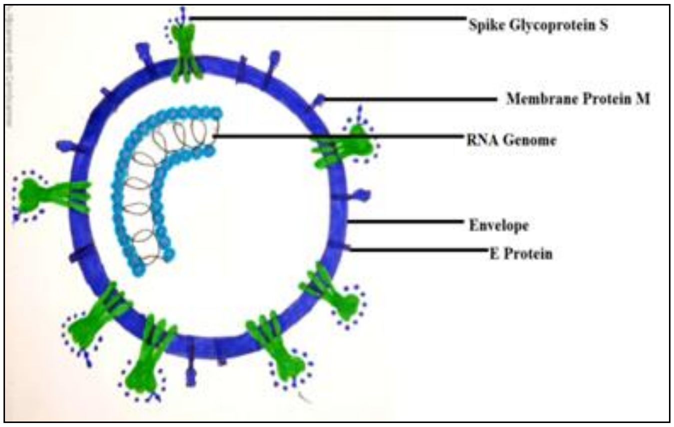

FIG. 1: STRUCTURAL BIOLOGY OF VIRUS

Virus Classification: [69, 70]

Realm : Riboviria
Phylum : Incertaesedis
Order : Nidovirales
Family : Coronaviridae
Genus : Betacoronavirus
Subgenus : Sarbecovirus
Species : Severe Acute Respiratory syndrome related coronavirus
Strain : Severe Acute Respiratory syndrome related coronavirus 2
Synonyms : 2019 nCoV"

Phylogenetics and Taxonomy: It is an enveloped virus with a "positive sense single stranded RNA (+ssRNA) virus" with a solitary RNA segment (genome) that occurs linear and a nucleocapsid having symmetry which is helical. The size of the genome coronavirus approximates from 26-32 kilobases, one of the biggest RNA family [71]. They show a typical club designed prominences exhibited from their outer surface, which in the electron micrograph generate a picture of solar-corona from which the name has been derived [72].

"Coronaviruses" form the sub-family of "Orthocoronavirinae" in the family of "Coronaviridiae" order nidovirus and the realm "Riboviria" [3, 73]. Like the SARS 2003 outbreak, it is a affiliate of the sub-genus "sarbecovirus" (beta CoV lineage B). The length of sequence of RNA is around thirty thousand bases. "SARS-COV-2" is distinctive amid the well-known "beta-coronaviruses" in its induction of a "polybasic cleavage site", a typically recognized to upsurge virulence and transferability in other viruses [74].

When adequate genomes sequences are available, it becomes feasible to rebuild a phylogenetic diagram related to the transmutation past of the virus family. Till 12th of January, 2020, 5 genomes of "SARS-CoV-2" has been extracted from Wuhan and updated by the Chinese CDCP and other institutional bodies, number of genomes raised by 42 from 30 on January 2020 [75].

After analysis of phylogenetic, the samples revealed that they were significantly identified with maximum 7 mutations traced to a shared ancestor suggesting the primary infection in humans was reported by the end of 2019. By March 27th 2020, 1,495 "SARS-CoV-2" genome samples on 6 continents were made available publicly [76].

By February 11th 2020, the "ICTV (International Committee on Taxonomy of Viruses)" declared that conferring to the present rules that sum up the ranked relations among "coronaviruses" based on 5 conserved nucleic acids arrangements, the disparity among what was assigned as "2019 nCoV" and the viral strain from 2003-SARS spread was not sufficient to convert them into different viral class. Therefore they started the 2019 "nCoV" as a strain of "severe acute respiratory syndrome" related coronavirus [77].

Life Cycle: The beginning of infection occurs when the glycoprotein of virus spike(s) adheres to its corresponding receptor of the host cell. After the addition to the protease of the host cell causes cleavage by activating the receptor adherent S protein. The host-cell protease guides the entry and activation permit the virus to make entry into the cell of the host by a process known as "endocytosis or direct fusion" of the viral envelope with the host membrane [78].

On the access in the host, the particle of the virus gets un-coated, and its genome makes entry into the cytoplasm of cell. The "coronavirus RNA genome" has a five methylated cap and a tail of polyadenylate, which facilitates the RNA to stick to host cells ribosomes for the process of translation. The translation of the host ribosome initiates over-lapping open interpretation of the frame to form a long polyprotein genome of the virus. This polyprotein has its particular proteases that slice the polyprotein into many non-structural proteins [79].

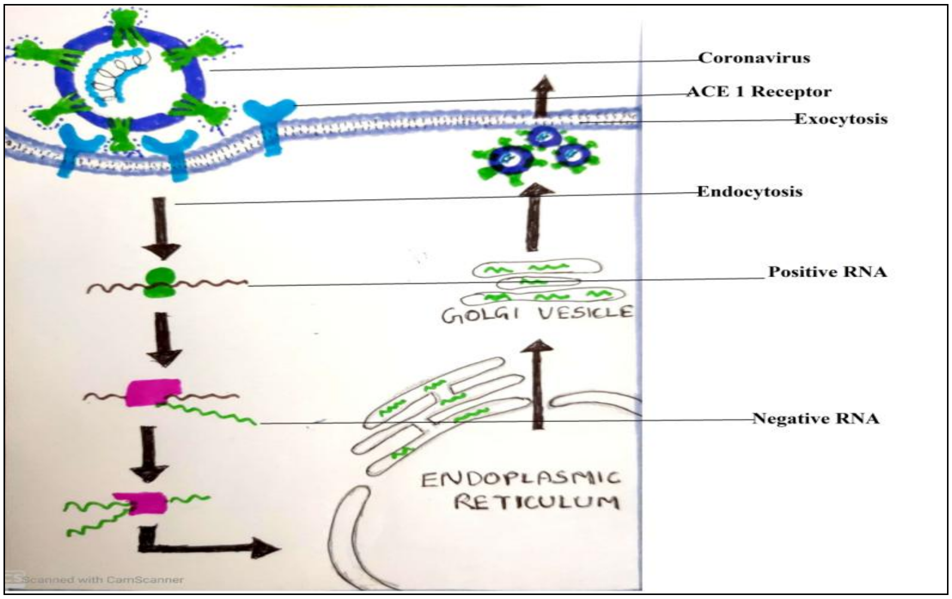

FIG. 2: PATHOBIOLOGY OF VIRUS

Replication: A large quantity of the non-structural proteins gather to produce a multi-protein "replicase transcriptase complex (RTC)". The principal RTC is the" RNA-dependent RNA-polymerase" (RdRp).there is a direct involvement in the transcription and replication procedure of RNA from a strand of RNA. The remaining non-structural proteins present in complex help in the process of transcription and replication. The exo-ribonuclease non-structural protein gives additional accuracy to replication by giving a proofreading purpose, which is lacked by the "RNA-dependent RNA-polymerase" [80].

The chief purpose of the complex is to promote replication of the genome of viral. This results in the "replication of positive-sense genomic RNA from the negative-sense genomic RNA". The added significant purpose of the complex is to transcription of the genome of viral. RdRp straightly meditates the production of the negative sense sub-genomic molecule of RNA from the RNA of a positive sense genomic. This is achieved by the transcript process of these negative sense sub-genomic molecules of RNA to their respective positive sense "mRNAs" [79].

Release: The genome of the young viruses is the replication of the positive-sense RNA genome. The m-RNAs acts as gene-transcripts of the distal 3rd of the genome of the viral after the first over-lapping reading frame. These m-RNAs are transformed by the ribosomes of host's into many accessory and structural proteins. Translation of RNA takes place in the "endoplasmic reticulum". The structure of viral proteins such as M, E, and S transfer into intermediate Golgi compartment. There the M-proteins govern maximum protein to protein connections requisite for the association of viruses after nucleocapsid binding. Secretory vesicles release progeny viruses by the process of exocytosis [81].

CONCLUSION: The novel coronavirus SARS-CoV-2 seems to defy all the laws of virology, posing the numerous challenges all over, to produce an effective vaccine, which indeed is the most effective way to counter challenge its demolishing potential besides the containment prologue! The constantly arising strains with renewed mutations emphasize the most upheld need of the hour that the vaccine, even if it is a long way to go before human trials begin, must provide long-lasting and effective immunity to each one of us on the planet. The pushing of the fundamental limits of knowledge is applicable now, where the researchers must combine the genomic data available so far with even astrophysical frontiers (to exemplify) where the new secrets of the Universe and extreme states of matter are often discovered for the first time!

Thus, it can be reaffirmed that with any battle on; the knowledge powerful will always give and lead the ways in the future!

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