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Mini Review

Evolutionary-scientific-cure[Esc.]:Part 1. Corona virus disease [CVD]

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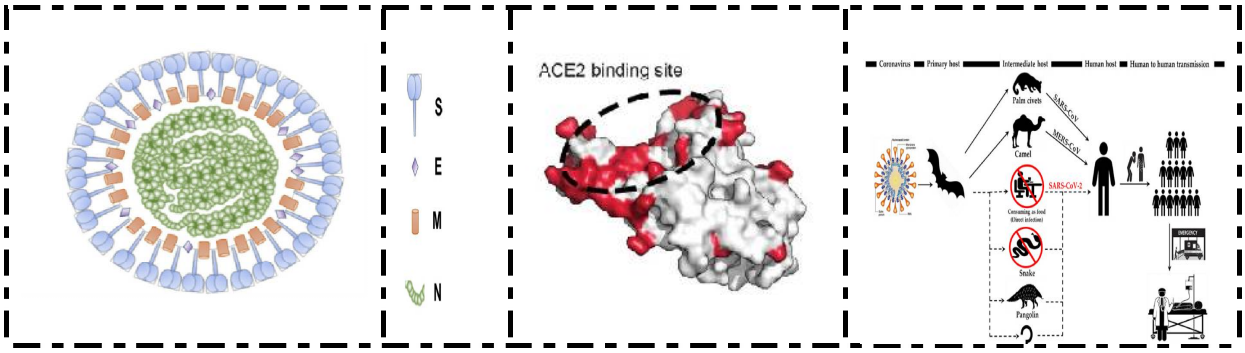
(Dedicated with profound respects to Dr P V Krishna Rao, former professor of Chemistry, Andhra University on his eightieth birth anniversary)

ABSTRACT

Corona virus (Cov) has a single stranded RNA genome in the nucleus. SARS-Cov-2 is the cause of pandemic this year infecting five million people spread all over the world during last four months. In spite of emergence measures, the death toll crossed three lakhs of infected ones. This virus enters human cell through ACE-2 with higher transmission rate and stronger binding compared to earlier SARS-Cov (Severe acute respiratory syndrome), which resulted in an epidemic in early 2000s. The virus infects well-differentiated human airway epithelial cell lines in vivo. The common clinical symptoms of COVID-19 (COrona VIrus Disease-19 or 2019) are fever, cold and dry cough, but leads to emergency for patients with severe infection or those suffering with comorbidities. Remdesivir is now in use with emergency authorization of FDA along with symptomatic treatment. Social distance and change of life style at work place are the measures for diminishing the spread of dreaded infectious disease. The research on specific new drugs, vaccines along with repurposing existing medicines is now a priority domain.

Graphical Abstract



Keywords: Corona virus- SARS-COV-2, COVID-19, Pandemic, Remdesivir, Social distance.

INTRODUCTION

Coronaviruses (CoVs) belong to the Coronaviridae family in the Nidovirales order. CoVs have large linear positive single stranded RNA genomes as nucleic matter with size ranging from 26 to 32kbs in length. It possesses crown-like spikes on the outer surface and thus called coronavirus. COVs comprise of four genera(Chart 1)viz. alpha-, beta-, gamma- and delta(**1-56**)

Chart 1. Virus classification

(unranked):	Virus
Realm:	Riboviria
Phylum:	incertae sedis
Order:	Nidovirales
Suborder:	Cornidovirineae
Family:	Coronaviridae
Subfamily:	Orthocoronavirinae

Genera
- Alpha-coronavirus
- Beta-coronavirus
- Gamma-coronavirus
- Delta-coronavirus

Human Corona viruses: α and β coronaviruses have the ability to infect even healthy humans of all age groups and ethnic origin. Of course, the casualty and severity increase with co-morbidities. Till last year, six human Corona viruses (HCoVs) were confirmed (Chart 1b). SARS-CoV 2 is the seventh CoV found causing severerespiratory distress in human subjects.It was proposed that multiple recombination events joining genome fragments ofdifferent bat SARSr-CoV origins culminated in the evolution into human SARS-CoV (Figure 1).

Chart 1b. Human Corona viruses

#	((HCoVs))	Coronavirus genus
1)	HCoV-NL63	alpha-
2)	HCoV-229E,	alpha-
3)	HCoV-OC43	beta-
4)	HCoV-HKU1	beta-
5)	SARS-CoV	beta-
6)	MERS-CoV	beta-
7)	**SARS-CoV-2**	**beta-**

Human influenzas

H1N1	**H**emagglutinin **N**euraminidases	2009 April

During the years 2002-3, SARS-CoV outbreak infected over 8,000 people with early-severe symptoms of respiratory discomfort right away. The transmission route of virus was from bats to humans through civets. In 2012, Middle East respiratory syndrome coronavirus (MERS-CoV) erupted in Saudi Arabia and most cases were in the Arabian Peninsula. It caused acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) leading to fatality due topulmonary failure. About 2,500 cases have been documented by January 2020 and around 35% of diagnosed patients died from it. These two epidemic incidents spurred deep research in virology.

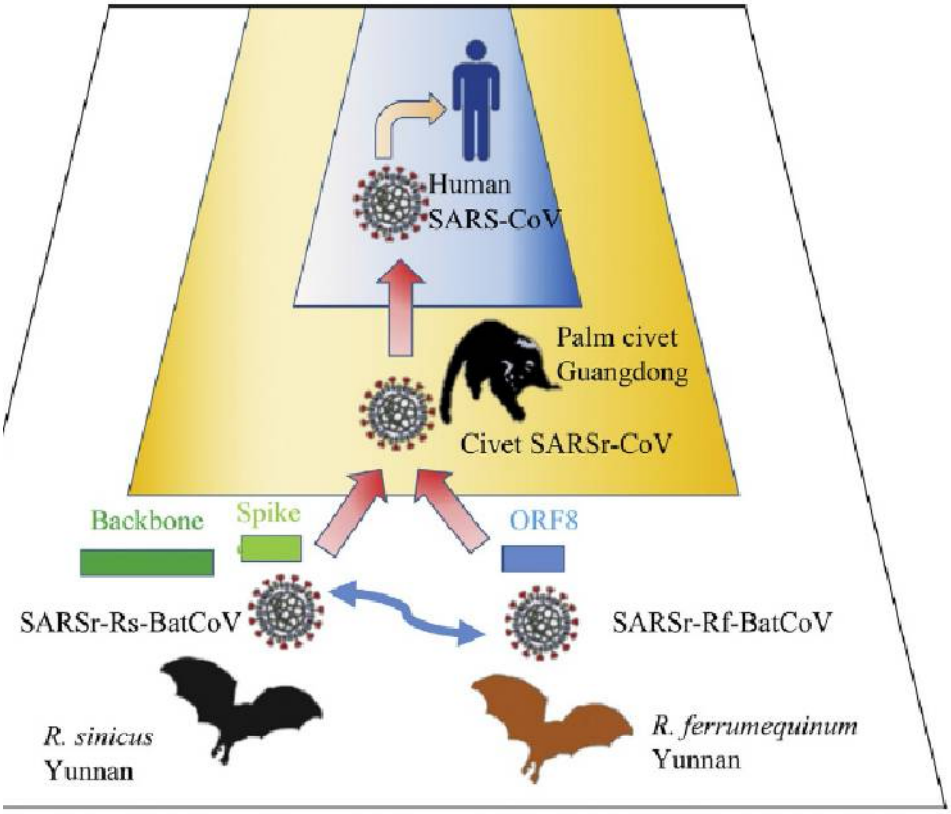
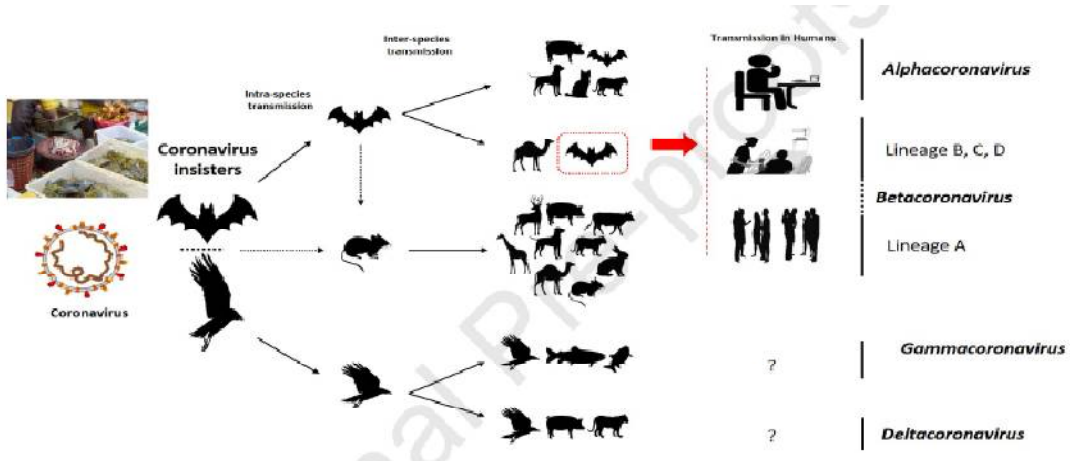


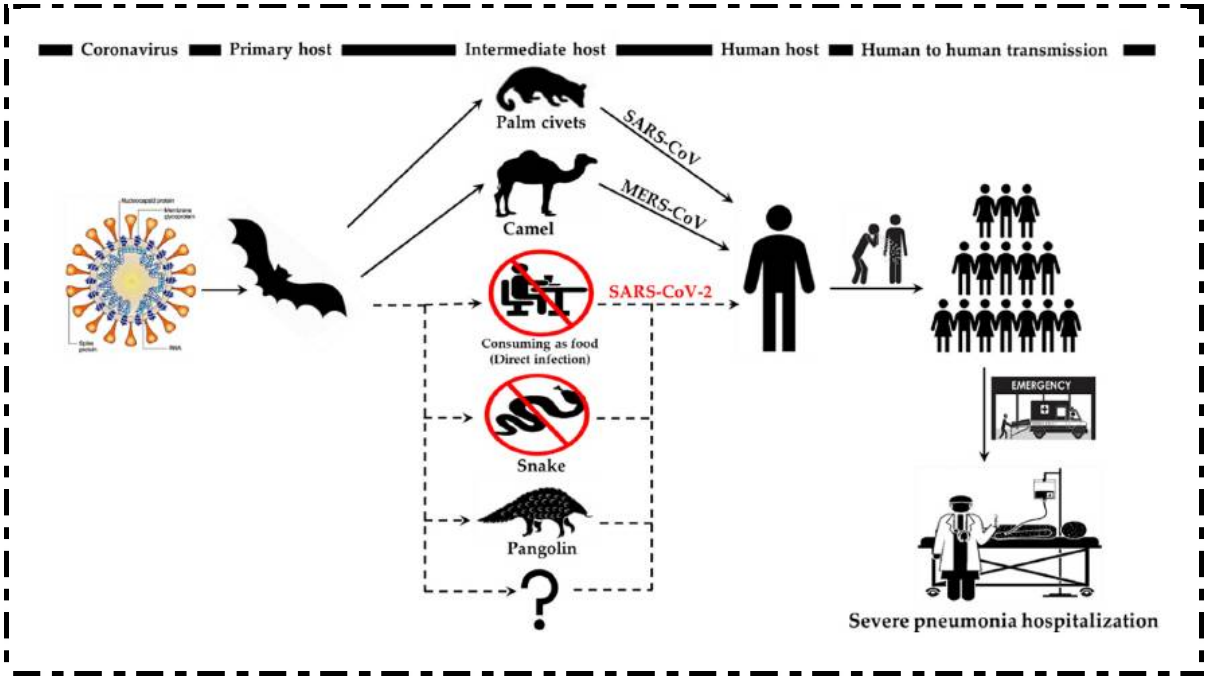
Figure 1. Overview of evolution of bat SARSr-CoV into human SARS-CoV.

Key reservoirs and mode of transmission of coronaviruses



Suspected reservoirs of SARS-cov-2 are red encircled);

Key reservoir and potential interspecies transmission routes of SARS-CoV, MERS-CoV and SARS-CoV-2



Emergence of new/unfamiliar pneumonia outbreak: A new disease was recognized when a cluster of people were hospitalized with severe pneumonia in 2019 December in Wuhuan, an emerging business hub of China.This virus killed a greater number of people inthe first fifty days of the epidemic.

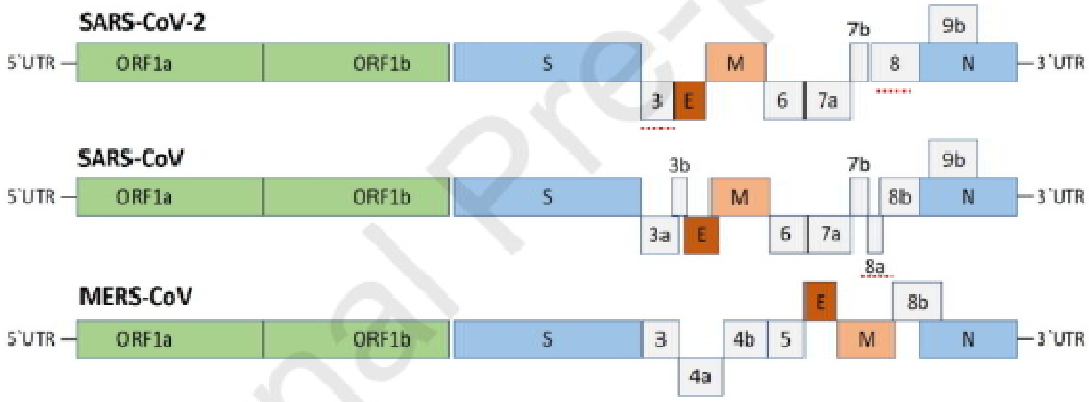
New Corona virus: From bronchoalveolar lavage fluid samples, from initial group of patients in Wuhan Jinyintan hospital from Wuhan, one more human Corona virus (2019-nCOv) was isolated. Using state-of-knowledge-tools, it is identified as beta corona virus 2b lineage in the phylogenetic tree. It had not been detected earlier in humans or animals. Initially World Health Organization (WHO) (on 7 January. 2019) named it as novel coronavirus (2019-nCoV).The results of sequencing the genome of new virus responsible for severe acute respiratory syndrome (SARS) turned out that 86.9% of the genome is the same as that of epidemic SARS-CoV and also there is 80% of nucleotide identity(Chart 2,). Based on it, International Committee on taxonomy of Viruses named the new pandemic human infecting agent as “severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) on 11th Feb 2020.The World Health Organisation (WHO) coined an abbreviation COVID-19 (COrona VIrus Disease-19 or 2019) (Figure 3) for the new disease.

Structure of SARS-CoV-2: RNA genome of SARS-CoV-2 contains29,811 nucleotides encoding 29 proteins. The four structural proteins are S (spike), E (envelope), M (membrane), and N (nucleocapsid), playing diverse important roles (Figure 2).

Chart 2: Key variation of protein between HCov : [SARS-CoV-2; SARS-CoV ; MERS-CoV] [red Square]

- 5'-Untranslated region (5'-UTR)
- Open reading frame (orf) 1a/b (green box) encoding
- Non-structural proteins (nsp) for replication
- Structural proteins including spike (blue box)
- Envelop (maroon box)
- Membrane (pink box)
- Nucleocapsid (cyan box) proteins

☞ Accessory proteins (light grey boxes)
- o orf 3 6 7a 7b 8And 9b in the SARS-COV-2 genome
- o 3'-untranslated region (3'-UTR).



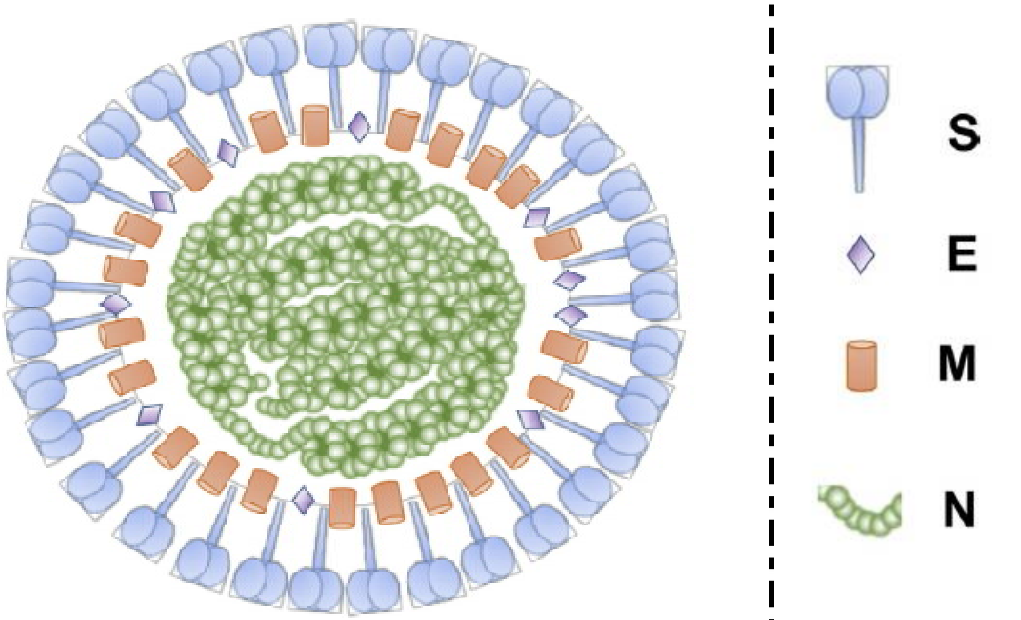


Figure 2. Diagrammatic representation of coronavirus virion.
S, spike protein; E, envelope protein; M, membrane protein; N, nucleocapsid protein encapsidating RNA genome

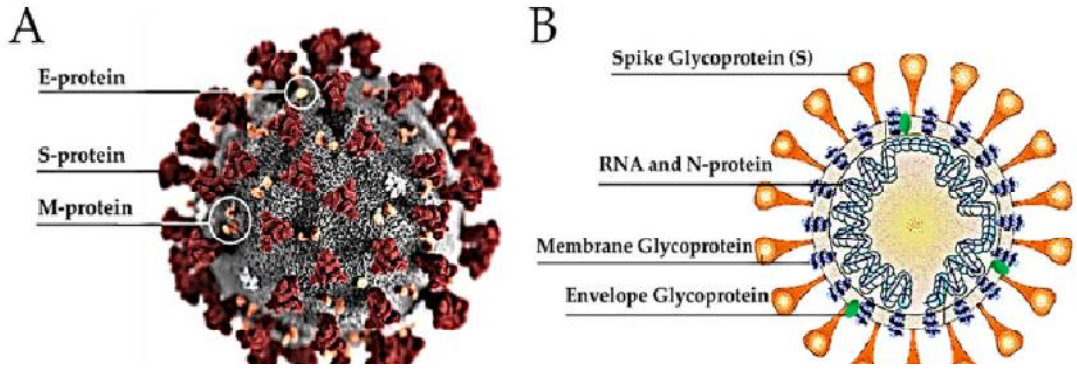


Figure 2b. SARS-CoV-2 virion created at Centers for Disease Control and Prevention (CDC)

Structure of SARS-CoV-2.

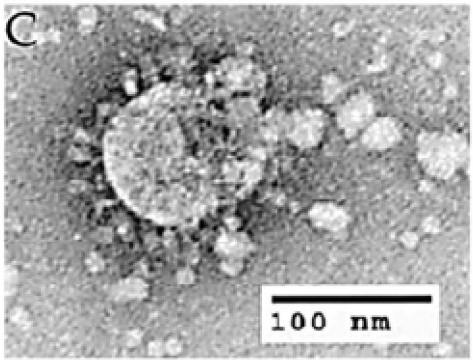


Figure 2c. Electron microscopic image of a thin section of SARS-CoV-2 within the cytoplasm of an infected cell
spherical particles through the viral nucleocapsid

Pandemic: Since the first few cases detected in Chinaduring December 2019, the United States has become the most-affected country with more than 15 lakhs of diagnosed cases and three lakhs deaths.The data compiled by the Center for Systems Science and Engineering at Johns Hopkins University recorded more than 5 million people across the globe have been diagnosed with COVID-19 pandemic and three lakhs of fatalities till 20th May, 2020(Chart 3).The data available appears on lower side of actuals due to limitations in adaptive testing protocols, dynamic nature of spreading profile of virus and un-noticed cases.

Chart 3. Pandemic infection score (20th May, 2020)

SARS-CoV-2

	Infected	Deaths	Recovered
Total	50,00,561	3,28,172	18,99,675
USA	15,81,903	93,806	3,01,341
China mainland	82,967	4,634	78,249
Wuhan, Hubai	67,803	3,212	64,014

SARS-CoV-2

Country	Infected	Country	Infected
Russia	3,17,554	U K	2,48,818
Brazil	2,93,387	Italy	2,27,364
Spain	2,78,803	India	1,12,359

Transmission among human subjects: The virus in an infected person is most often transmitted to another human being through respiratory droplets while sneezing and coughing. The continuous close contact of health care staff and doctors with patients at varying stages of progress of disease is another fierceful mode of transmission with life threatening consequences.

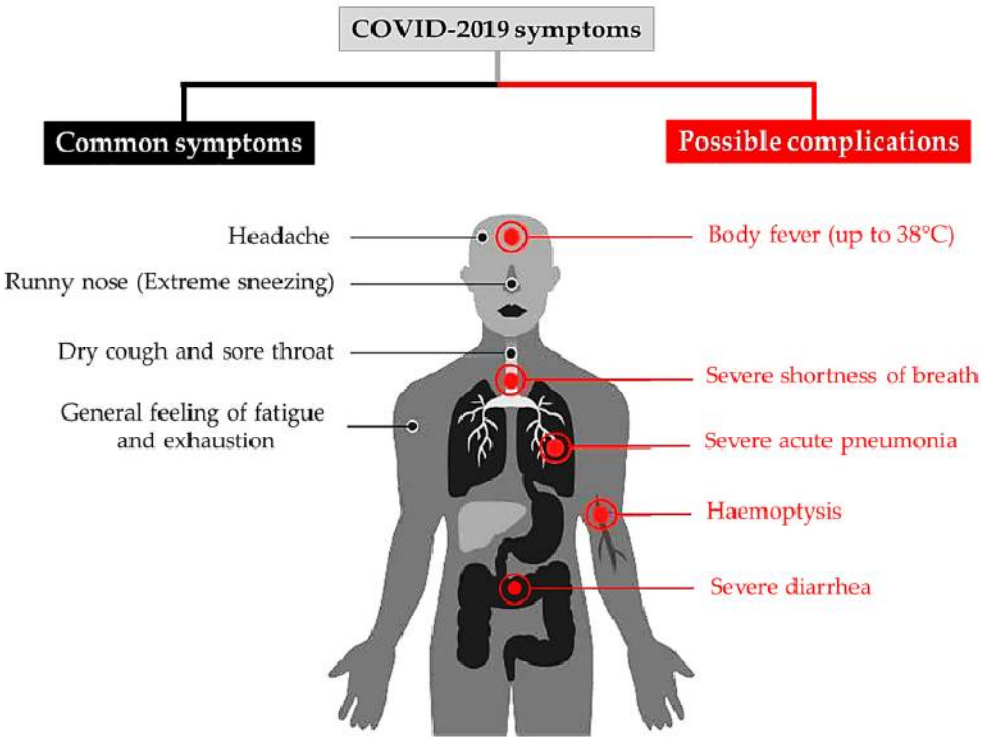


Figure 3. Common symptoms and possible complications of COVID-19 (WHO)

Transmission of virus from mother to offspring: The frequency and severity data of the infection by perinatal and postnatal routesis scarce/sparse and thus not completely delineated/understood. Yet there are instances describing transmission of COVID-19 to the fetes. Breast milk acquisition of infection has not been recognized to date, but strategies to ensure safety of infants are need of the hour.

Interaction of virion and host cell in vivo of healthy human subject: The process is initiated by the attachment of S protein of virus to specific receptors of cells in vivo (Chart 4). The host tissue susceptibility depends on the availability specific receptors for infectious virus.

Chart 4.	Receptor in human cell	Coronavirus
ACE2	Angiotensin-converting enzyme 2	o SARS-CoV-2 o SARS-CoV o HCoV-NL63
DPP4	Dipeptidyl peptidase-4	o MERS-CoV
APN	Aminopeptidase-N	o HCoV-229E

Entry of SARS-CoV2 into human cells: SARS-CoV2 utilize human AEC2 for viral entry (Figure 4) and infect well-differentiated human airway epithelial cell lines in vivo. Its journey begins in the

first days after infiltration from the upper respiratory tract. Coronavirus spike (S) glycoproteins promote entry into cells and bind with high affinity to the angiotensin-converting enzyme 2 (ACE2) receptor in humans. The transmissionrate of SARS-CoV-2 is found to be higher than that for SARS-CoV. and the reason could be the genetic recombination event at S protein in the RBD region. Following receptor binding and fusion of viral and cellular membranes, the coronavirus genomic RNA is released into the cytoplasm of host. The replication process is describedin chart 5and figure 5b.

Chart 5. The life cycle of SARS-CoV-2 in human host cells

- S1 region (N-terminal) subunit of S specializes in recognizing ACE2 and binding to the host cell receptor
- Conformation change in the S protein → facilitates viral envelope fusion with the cell membrane through the endosomal pathway S2 region (C-terminal) subunit of S. It is responsible for membrane fusion region
- SARS-CoV-2 releases RNA into the host cell.
- Genome RNA is translated into viral replicase polyproteins pp1a and 1ab
- pp1a and 1ab cleaved into small products by viral proteinases
- Polymerase produces a series of subgenomic mRNAs by discontinuous transcription → Translated into relevant viral proteins
- Viral proteins and genome RNA are assembled into virions in the ER and Golgi
- Transported via vesicles
- Released out of the cell

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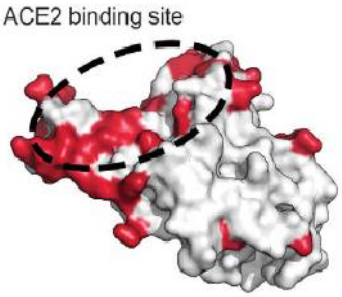
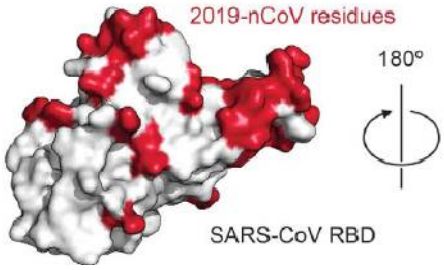
The release of newly assembled virions usually starts 3–4 h after initial infection

Blue: ACE2;
tan, pink, green:
S protein protomers





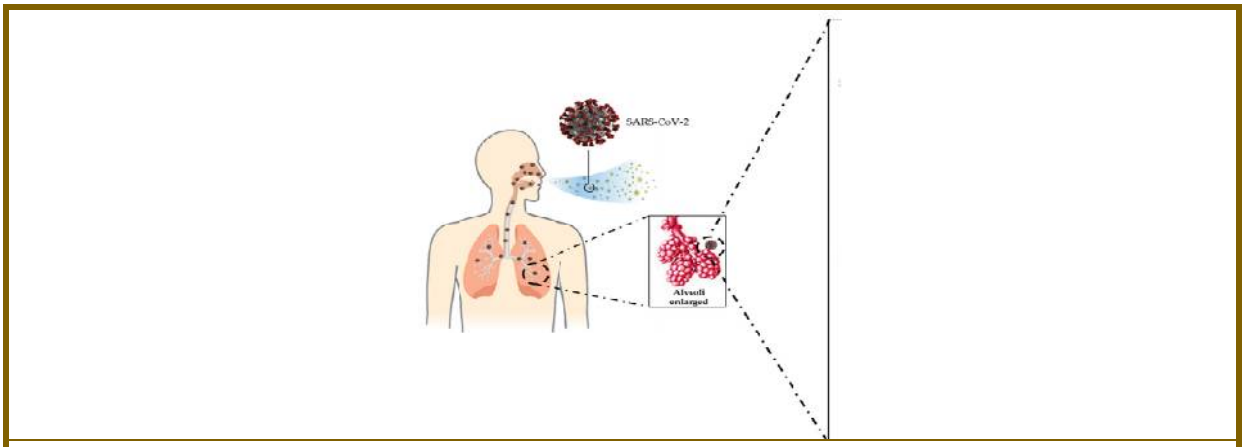


Figure 4. 2019-nCoV S binding to ACE-2

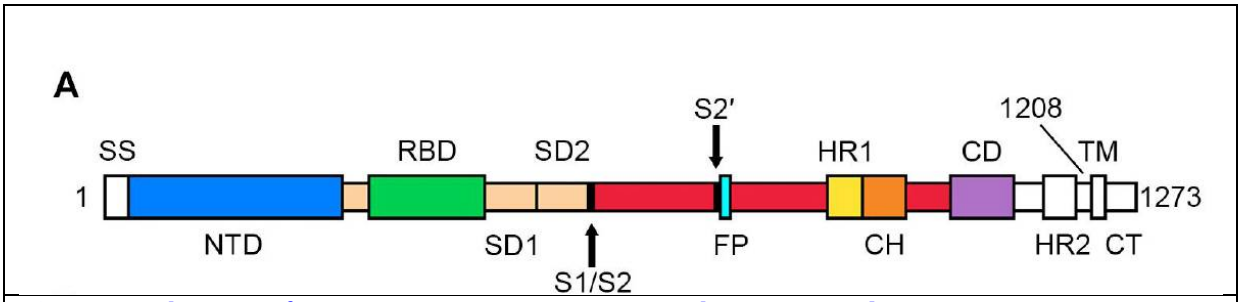
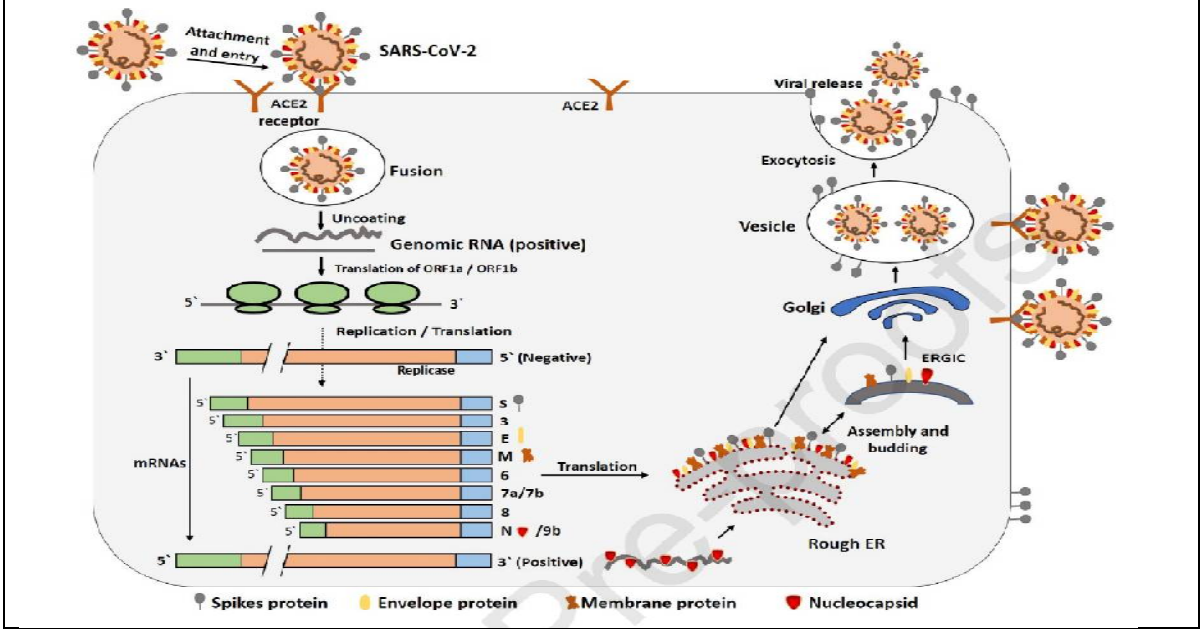


Figure 5. Schematic of 2019-nCoV S primary structure white. SS, signal sequence; S2′, S2′ protease cleavage site; FP, fusion peptide; HR1, heptad repeat 1; CH, central helix; CD, connector domain; HR2, heptad repeat 2; TM, transmembrane domain; CT, cytoplasmic tail. Arrows denote protease cleavage sites.

Figure 5b. Replication of SARS-CoV-2 in human lung cells



Incubation period of SARS-CoV2 in humans: The incubation period after infection in most patients varies from 1 to 14 days with a median of five days. But, longertime (24 days) period is not rare.

Symptoms COVID-19: Most common symptoms are fever, common cold, dry cough and tiredness (Figure 3). The shortness of breath, chest pain or pressure are attention drawing parameters for hospitalization (Chart 6). But, some people even after onset of covid-19 remain asymptomatic. It is alarming for health care personnel that these subjects are potential transmitters of this devasting infectious disease. Many will develop mild to moderate illness and appear to recover without hospitalization.

Chart 6. Clinical symptoms of Covid-19

Less common symptoms		**Co-morbities**
☞ Aches/ pains	☞ Headache ☞ Confusion	☞ Hyper tension (HT or HTn) ☞ Diabetes mellitus (DM) ☞ COPD (Chronic obstructive pulmonary disease) ☞ CVD(Cardiovascular disease)
☞ Sore throat	☞ Loss of o Taste/ smell o Speech ☞ Movement	
☞ Diarrhea	☞ Rash on skin ☞ Discoloration of fingers/ toes ☞ Bluish lips/ face	
☞ Conjunctivitis		

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Diagnosis: The disease being asymptomatic too, the prima facie evidence is taken from travel history (national/international) and comprehensive contact of a person with patients proved to be Covid-19 positive. The gold-standard-clinical test for Covid-19 confirmation is molecular (RNA) detection with RT (reverse transcription)-PCR or real-time RT-PCR. The nasopharyngeal swab, sputum, deep tracheal aspirate or bronchialveolar lavage samples collected from infected suspect patients are used for ascertaining covid-19 positive cases. The entire course of treatment is in isolated protected wards of labelled hospitals. Another test for COVID-2019 is with olfactory epithelium from the nasal cavity tissue. The advantage of it is detection of COvid-19 prior to onset of symptoms or even in asymptomatic patients.

Recovery time of Covid-19 patients: From electronic records of hospitals over last few months, the recovery period observed is around 2 weeks if disease conditions are mild. However, it extends to 3-6 weeks for patients with severe or critical disease progress or when co-morbidities emerge. Unfortunately, relapse has been observed in patients discharged after passing through confirmatory test protocols for absence of disease-causing virus.

Drugs for SARS-CoV-2 infected patents: There is not even a single (FDA) approved drug till now to treat patients suffering with dreaded infectious Covid-19.Mostly symptomatic treatment protocols in vogue are adaptively practised. Remdesivir (Figure 6) is an FDA approved antiviral drug developed by Gilead to target the Ebola virus,. Phase III clinical trials have been started to see if this drug could treatSARS-CoV-2 infection also. FDA's emergency authorization of remdesivir is a bliss in treatment options to COVID-19 patients in record time.

REMDESIVIR	
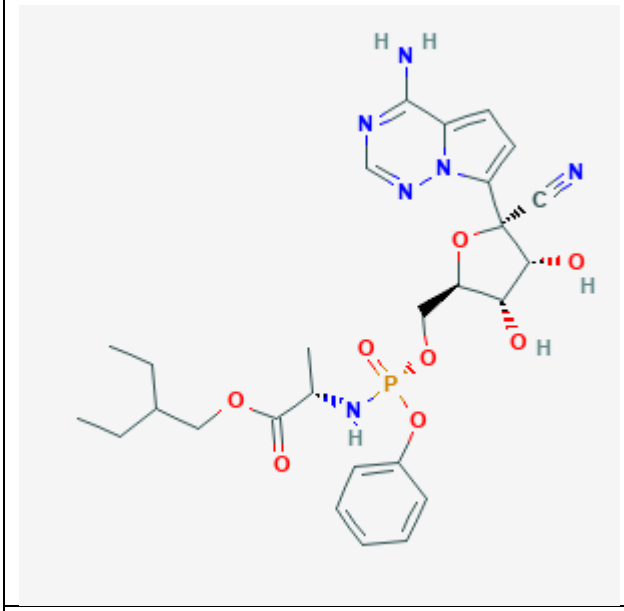	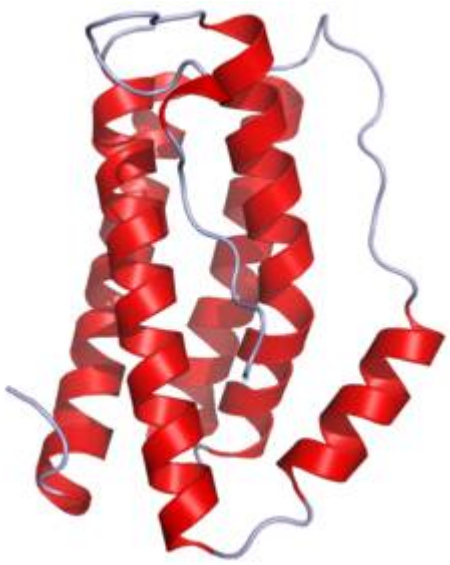
Figure 6. IUPAC Name: 2-ethylbutyl (2S)-2-[[[(2R, 3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy-henoxyphosphoryl]amino]propanoate	IL6 (Interleukin)

Keeping aside the facts and figures of what we do know (Chart 7) and do not know about the use of antimalarial treatments in this alarming scenario, judicious application of other proven drugs like chloroquine and hydroxy chloroquine is underway. Similarly, IL6 (Interleukin) (Figure 6) inhibitors (arthritis drugs), might be of relief for most severely affected or end-of-life stage patients.Repurposing drugs is another active intelligent research paradigm now addressing the choicest medication in the present blurred scenario.

Chart 7. Categories of therapies
☞ Preventing the viral RNA synthesis and replication
☞ Blocking the virus from binding to human cell receptors
☞ Restoring the host's innate immunity
☞ Blocking host's specific receptors or enzymes

Reproductive number (R0): The rate of infection (number of secondary infections arisen) in a patient by a virus is called R0 (KB 1). The factors affecting the information are innate properties of the virus, and the amount/duration of contact of infected patient with healthy subjects. The preliminary estimate of R0for SARS-CoV-2 infection is in between 1.3 and 6.5 with an average of 3.3. It suggests a higher pandemic potential of SARS-CoV-2compared to SARS-Cov.

KB (Knowledge bits) 1: Interpretation of R0				
If	R0 is >1,		If	R0 is ≤1
Then	infections will continue to spread		Then	infection will eventually diminish

.

Protocols for prevention of spread of pandemic infection: Vaccines, change of life style at home and work place (Chart 8), governess implemented sanctions/strictures/taboos will combat with deadly

life-threatening virus for 'greatest benefit to mankind' by living normal expected life on mother (planet) earth.

Vaccines: Vaccines are not available obviously, although they play a key role in preventing healthy and also risky individuals with co-morbidities from attack of infection, the development of vaccines for women of child-bearing age is of high priority, not only to protect the pregnant patients but also to safeguard the health of the fetes and new-born infants. It enhances pre- and post-natal health care system to safeguard next generation of humankind.

Chart 8. Precautions at workplace

- Monitoring parameters before going into work
  - Temperature
  - Flu symptoms
- Wearing a mask
- Maintaining social (six-foot) distancing from others
- Disinfecting and cleaning workspaces regularly
- Cleaning hands with
  - Alcoholic sensitizer
  - Soap water
- Confining to four-wails or green zones
- Avoiding
  - International/ domestic travel
  - Dense (social) congregations
- Regular cleaning of
  - Frequently touched surfaces

Facts-fears-future (Fcube): The disastrous effects of Covid-19 on survival/health/ comfort/mental peace/ mode of life style of humankind and economy of states/governess are unprecedented after plague wave in the history of mankind. The scientific progress in combating COVID-19 during these five months is noteworthy. The benefits of results arrived at made a mark and have been possible as a result of concerted efforts multi-talented experts keeping aside of their ongoing projects. They researched with a single motto of benefit to mankind with no objective of returns including name and fame. The knowledge bits (to be tested rigorously) sparkled through scientific pursuit in basic understanding of virus life cycle will evolve to develop new strategies to mitigate the pandemic infection and death toll.

According to Kyle-Sidell, working at a New York City hospital, it's hard to switch tracks when the train is going a million miles an hour. COVID-19 being an entirely new devastating disease, the focus of scientific research is around improving understanding of the virus and implications of disease. This leads to surge of new strategies for clinical tests, treatments, and vaccines to mitigate illness and death.

The pandemic may change the way of virus mutation in time and surroundings. The future evolution, adaptation, and spread of this virus warrant fast but in depth multifaceted investigations to maximize the likelihood that effective weapons will be available against unknown diseases that might emerge in the future.

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