CORONA VIRUS - ITS ORIGIN, REPLICATION AND REMEDY FOR FUTURE THREAT

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A new coronavirus (2019-nCoV) infecting humans have emerged in Wuhan, China in late 2019 and is now the most current topic not only in India but also throughout the world. Its genome has been sequenced and promptly released the genomic information. In this article the different aspects of the virus including the habitat of virus have been discussed. The method of the spread of virus and its way of identification have also been described. Lastly, the cause and remedy of spread of disease as pandemic has been elaborated.

The present widely spread Corona Virus was first detected in Wuhan district of China as the disease was found widely in this district for the first time in the month of January 2020. This virus was initially named as 2019 nCoV or Wuhan Corona virus. The popular name of the virus is now SARS-CoV-2 or Corona Virus and the disease is known as COVID -19 or CoV-19 which is now pandemic due to spread of the disease throughout the world.

Generally, various types of corona viruses are found that cause respiratory disease to birds and mammals including humans. These viruses are a group of related viruses that originated from very early days starting from HCoV- N163 (560 to 820 years ago) to HCoV- 229E (about 200 years ago) to HCoV – OC43 (about 120 years ago) to HCoV – HKU1 (early 1950) to SARS – CoV (4 to 17 years before SARS epidemic in 2002) to MERS - CoV (about 2006) and finally to the present SARS-CoV-2². It has been established that the actual origin of present corona virus was from Bat to Asian Palm civet as SARS- CoV in one direction and in other direction from Bat to MERS – CoV via Camel. Probably the recent one n

CoV 2019 was also originated directly from Bat², as shown in figure 1 where the intermediate host is still not known. However, Cyranoski² reported that pangolin is believed to be the intermediate host of SARS-CoV-2. But one point has been raised whether this virus was spread due to leak from a biowar laboratory. Many have raised a question whether this present corona virus was synthesised in a bio-war laboratory in Wuhan of China or due to leak from the Bio-war laboratory of Wuhan.

Generally this type of virulent virus was kept under the most secure condition as Biosafety level 4 (BSL-4) in any research laboratory. So the chance of leakage is very less. Wuhan Institute was officially recognised as one of the eight bio-warfare research laboratories of the world by the Biological Weapons Convention (BWC) probably in 1993. The leakage news was not confirmed.

However, scientists of some countries have not ruled out the possibility of synthesis of this virulent virus just like any germ warfare from the laboratory of Wuhan. This was also not confirmed but scientists Kristian G. Andersen and others³ from different laboratories of USA, UK and Australia in February 2020, showed through their molecular biology studies that genomic evidence does not support that this virus Cov 2019 is the laboratory construct from an existing SARS-related corona virus. Corona viruses (CoV or SARS-CoV-2) are called zoonotic pathogens¹ as they

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are widely distributed among mammals and birds. Another special characteristic of this virus is that they require hosts for their growth and replication i.e., parasitic in nature. The name corona virus was derived from the Latin word *corona* meaning crown which refers to the appearance of crown or solar corona round the virus particles (Virions) which can be seen under the Transmission Electron Microscope. They are classified into four genera like Alpha, Beta, Gamma and Delta. Of them Alpha, and Beta CoVs infect mammalian hosts including human for their transmission and Gamma and Delta CoVs are restricted to infect birds.4

The present corona viruses are spherical with average diameter of 78 nm with several club shaped projections called spike about 20nm long on the surface of the envelope of protein coat of the virus called Capsid with single stranded RNA at the centre. RNA genome of these corona viruses is exceptionally long as compared to other RNA viruses with maximum size of 34 kilobases (34 kb) with high replication fidelity5.

The membrane of all corona viruses contains at least three viral proteins. These are spike (S), the type I glycoprotein that forms the peplomers on the virion surface giving the virus its corona or crown like morphology observed under the electron microscope; the M protein that spans the membrane three times and has a short N-terminal ectodomain and a cytoplasmic tail; and small membrane protein ( E ), a highly hydrophobic protein. The E protein of Avian IBV (Infectious Bronchitis Virus) has a short ectodomain, a transmembrane domain and a cytoplasmic tail. The E protein of the murine corona virus MHV (Mouse Hepatitis Virus) is reported to span the membrane twice, such that both N and C termini are on the interior of the virion v. The most prominent of these is the S glycoprotein (found in the spike) which is a major antigen responsible for binding with the receptor and cell fusion with the host cell membrane. The M protein is responsible for giving the shape of the virion envelope and is also playing an important role in virion assembly. A few corona viruses have another type of glycoprotein Haemaglutinin – Esterase (HE). The viral genome is associated with another basic phospho protein called Nucleocapsid protein (N). The RNA genome is non-segmented positive single stranded RNA of about 26 -34 kb with 7 – 10 different open reading frames (ORF). The corona virus RNA protein complexes are quite sensitive to the action of ribonucleases4,7

RNA viruses have one special characteristic that they can accumulate considerable genetic diversity in a very short period of time. The occurrence of high genetic diversity in viruses is due to their high rate of mutation and also having high replication fidelity causing an expansion of the genome leading to an increase in adaptation to its host. The high mutation rate in RNA viruses will give increased population fitness helping them to aggravate infection to human. It is also important to note that the high rate of replication of Corona viruses (RNA virus) would come at a cost as the replication occurs, as if without any proof reading, due to lack of enzyme exonuclease in RNA polymerase causing a slow-down of growth after a short period of time4.

**Infection and Replication of Corona Virus on the Host Cell**

The infection is initiated by the binding of corona virus to the receptor of the host cell (human) and entered the cell through endocytosis and fusion of membranes. Many corona viruses utilize peptidases as their cellular receptor. Alpha corona viruses utilize aminopeptidase N (APN) as their receptor, SARS-CoV and HCoV- NL63 use angiotensin-converting enzyme 2 (ACE2) as their receptor. As the RNA genome of this virus is positive single stranded RNA so it serves as the first mRNA of infection in the infected human cell. The first gene to be translated is the viral RNA polymerase called replicase followed by the translation of full length negative strand of the genome (antisense RNA). Using these strands as templates, they then produce progeny genomes and large number of sub-
genomic mRNAs. The next step in the coronavirus life cycle is the translation of the replicase gene from the virion genomic RNA. The replicase gene encodes two large ORFS, repla and replb, which express two co-terminal polyproteins, pp1a and pp1ab. These polyproteins are subsequently cleaved into the individual nsps. Coronaviruses encode either two or three proteases that cleave the replicase polyproteins. They are the papain-like proteases (PLpro), encoded within nsp3, and a serine type protease, the main protease, or Mpro, encoded by nsp5. These mRNAs produce structural proteins and accessory proteins through translation. The structural proteins M (Membrane protein), S (Spike protein) and E (envelope protein) are inserted into the endoplasmic reticulum (ER) and assemble in the Golgi and then accumulate in the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). Another protein produced is N protein that encloses the progeny genomes to produce Nucleocapsid and these coalesce with membrane bound components by budding into ERGIC to form virions. Ultimately the virions are transported to the plasma membrane via Golgi sacs or smoothwalled vesicle. These unassembled S proteins help in the fusion of an infected cell with adjacent new cell and thus enabling the infection to spread quickly from one cell to another. SARS-CoV2 has new biological characteristics as it can grow at 37 degree centigrade under cultural conditions whereas other corona viruses grow at lower temperature. The S protein is considered to be the most promising targets for corona virus vaccine development.

Human to Human transmission of corona virus mainly occurs through close contacts via respiratory droplets generated by sneezing and coughing. The virus spreads not only through droplets from sneezing and coughing but also through touch of a surface contaminated by virus-containing droplets and also through contact of a person having travel history from affected countries. The symptoms of this disease resemble other respiratory infections with coughing and fever and shortness of breath. Some patients have vomiting and diarrhoea. In the most acute cases, severe acute respiratory syndrome occurs with pneumonia and kidney failure leading finally to death. Generally symptoms begin after exposure from 2 – 14 days with an average of 5 days.

Figure 2. Replication of Corona virus (Taken from The Mol, Biology of Corona Viruses, Advances in Virus Research, Vol.06, Reference 2).
According to many experts, the first infected person may have some association with live animals or have taken some exceptional animal foods from Sea food market of Wuhan district of China, a city of more than 11 million people with a major transportation hub. Thus the disease was first spread from animal to human through contact then it was spread widely as pandemic from human to human which occurred first in China followed by South Korea, Italy, Spain, Iran, UK, United States, India and finally throughout the world\textsuperscript{10}. The mode of spreading of corona virus is different from Dengue and Chikangunya as they cause outbreaks through a carrier mosquitoes but corona virus spreads fast and they can do human-human transmission without any carrier. Thus to tackle the disease initial management is easy by way of isolating the patient. With the large scale outbreak the need of good infrastructure, isolated hospitals, trained doctors, trained health care staff, quarantine arrangement etc. are necessary. Indian Government along with all state Governments have taken a very good step from the very beginning to prevent spread of the disease with good management on all spheres to tackle the situation.

Some Indian microbiologists including Professor J. S. Virdi, an eminent microbiologist and K. K. Agarwal, President, Health care Foundation of India are of the opinion that India has an innate natural defence against deadly corona virus in the coming summer with high temperature and humidity. From the news in the journal Science of April 11, 2020, it has been noted from the findings of research work done in Johns Hopkins University\textsuperscript{11} of United States along with two MIT post doctorate students that the maximum number of corona virus transmissions is occurring in regions that had temperatures between 3 and 13 degree centigrade. This pattern is also found in the southern states of United States like Texas, Florida and Arizona showing a slower rate than northern states like Washington, New York and Colorado. The research groups of Beijing University also showed that hot and humid climate have a slower rate of spread than cold and dry ones. However it was not confirmed by any published data.

**Realistic Situation within the Population**

To understand the epidemic potential of corona virus the assessment of the basic reproduction number of the virus which is called Ro (R naught)\textsuperscript{9,12} is urgently needed. When an infected person enter a susceptible community or the infected person in a community, the measurement of Ro in that region gives the transmission potential of the virus in that area (Figure 3). In other words the potential spread of the disease or intensity of the outbreak can be understood from the value of Ro. If the measure of transmission potential is lower than the basic reproduction number (Ro) then it means that some people have been vaccinated or treated with some medicine against the disease or have acquired immunity due to exposure with pathogen. Thus the measurement of Ro gives a more realistic situation within the population. The value of Ro depends on the susceptibility of the population. The susceptibility of the population depends on their nutritional status and strength of immunity. It is also affected by the environment for instance, demographics, socio-economic and climatic factors. The Ro for Corona virus SARS-CoV 2 is between 1.5 and 3.5.

If the value of Ro is less than 1 showing existing infection causes less than 1 or in other words the disease will decline.

If Ro is 1 meaning thereby that the virus is still alive infecting one person.

If Ro is more than 1 showing disease will spread between people and there may be an outbreak. The value of R\textsubscript{0} for other epidemic viruses is given below.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Reproduction Number (R\textsubscript{0})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebola</td>
<td>1.51 – 2.53</td>
</tr>
<tr>
<td>H1 N1 Influenza 2009</td>
<td>1.46 – 1.48</td>
</tr>
<tr>
<td>Seasonal Influenza</td>
<td>2 — 3</td>
</tr>
<tr>
<td>Measles</td>
<td>12 — 18</td>
</tr>
<tr>
<td>MERS</td>
<td>around 1</td>
</tr>
<tr>
<td>Polio</td>
<td>5 — 7</td>
</tr>
<tr>
<td>SARS</td>
<td>&lt; 1 — 2.75</td>
</tr>
<tr>
<td>Small Pox</td>
<td>5 — 7</td>
</tr>
</tbody>
</table>

Very few research has been done on new disease COVID 19 but still some measures have been suggested by different scientists and from WHO that travel restrictions, social distancing and self quarantine efforts will reduce the spread of the disease.

**Remedy for Future Threat**

(i) **Restoring the homeostasis of ecosystem**

It has been well established that most of the infectious diseases to human being like AIDS, EBOLA, Bird’s Flu, MERS and Severe Acute Respiratory Syndrome (SARS) and the present SARS-CoV-2 (COVID 19) have originated from the zoonotic RNA viruses harbouring
mainly on animal. Bats¹ which can be called the natural reservoirs of wide diversity of Corona viruses including the present corona virus SARS-CoV². Again Bats are the only mammals that fly and they are most numerous after rodents (rat family). Due to deforestation Bats are coming nearer to human habitat posing serious threat to human health. Viruses causing Ebola, SARS, NIPAH, MERS and the latest Covid-19 are believed to reach humans from their natural home of bat bodies. Bats eat insect and fruits. As the forests become lesser and lesser bats have to fly for longer distances for food. So they are coming closer to human habitats¹³ or to the animal farm house which is also near the human habitat. When a bat sits on a tree to eat fruit or to an animal shed for insect, it leaves traces of its body fluids. When persons come in contact with such trees, fruits, animals or shed, they become victims of deadly viruses that might have left in these places. During SARS outbreak, the transmission occurs from bats to human through civet cats and during MERS outbreak it occurs through camel as an intermediate host. So bats have large number of viruses for which humans have no immunity. It is the human being that is responsible for spreading so much deadly viruses by destroying the natural habitat of animals¹³ as throwing stones in a beehive and let loose the bees (viruses).

During study of epidemics of SARS-CoV in 2002 and 2003, it has been established that the transmission of SARS-CoV 2 to human is done through markets of wild animals of Wuhan in China selling the meat of civet cats, rodents, dog, pangolins etc. and thus becoming the first epicentre of corona virus. This market is also well known as Wet Market. So the corona virus uses these animals of the market as vectors for their transmission to human. From the journal Week of February 9, 2020 it has been known that meat of some wild animals like deer, fox and crocodile are also sold in the local market and is traded and trafficked for human consumption to other countries.

From the detailed study of corona virus lineages, it has been noted that corona viruses are older than other viruses found in other animals and the present SARS corona virus is derived directly from wild animals in wet markets of Wuhan district of Southern China. The wide use of domesticated and wild animals as food for long time by human slowly changes the ecosystem of the virus. It will not be unwise to think that the origin of this type of virulent virus is due to the insatiable desire of human being to eat animals either wild or domestic. Another factor may also be due to the crowding of many animals¹⁰ in a small space of Farm house to make it an amplifier for viral pandemics. The outbreak of H5N1 Bird Flu in 1997 was originated in Chinese Chicken Farms due to crowding of chickens in the farms and also occurred in United States where Poultry farmers killed tens of millions of their birds to prevent the outbreak. In both these cases viruses did not jump into human population. The Bird Flu also occurred in India. Thus the Zoonotic viruses are giving us the alarm to take prevention against commercial farming of animals. Similar things happened in case of H1N swine flu outbreak in 2009, the epidemic is due to the confinement of pig in small places in North Carolina. Michael Gregor in his book ‘Bird Flu: Virus of Our Own Hatching’ warns that factory farming is a perfect storm environment for infectious diseases. He also said that “If you want to create global pandemics, then build Factory Farms”. In the editorial of the American Journal of Public Health in 2007 it was mentioned that our mass raising of animals and slaughtering of animals for food could be the genesis of the next big global pandemic. In addition, alteration in the environment occurred by land-use changes, logging or deforestation, expansion of agriculture and urbanisation into undisturbed areas as well as trade in wild life. All these lead to a change in the normal circulation of viruses and shifting of the behaviour of viral reservoir species like bats and other animals. The behavioural changes of virus and carriers lead to changes in transmission from human to human without using any intermediate host.

Thus to prevent the future global threat by similar new mutated more dangerous viruses than Corona the global conservation of ecosystem and reforestation is urgently needed. It has been accepted by many research scientists that the destruction of biodiversity and
ecosystem by man creates the condition for the emergence of new viruses and more dreadful diseases than COVID-19. In 1996 the emergence of Ebola epidemics in Baki and other villages of Africa, where about 90% of the people died in this disease by disrupting ecosystems through cutting forests, logging, mining, road building, bush meat hunting, butchering, killing animals and thus shaking viruses to lose from their natural hosts.

The traditional Chinese medicine is used for various types of diseases like arthritis, epilepsy, erectile dysfunction etc. by using extracts of body parts of different animals tigers, bears, pangolins, rhinos and others. This also increases the animal-human interactions causing changes in the ecosystem.

The health of all life in the planet is interconnected or in other words Human, Animal, Plant and Environment are all deeply connected and greatly influenced by human activities. Hence a multidisciplinary approach from experts in Plant and Animal ecology, Wild life management, Environmental Science, Conservation science, Social science, Forestry, Microbiology, Health science are needed. They will ensure public and planetary health before doing any deforestation, land-use changes and also to think for reforestation to re-establish the natural habitat of ethnic people and animals.

### ii) Human Population Control

The world population is increasing tremendously reaching already as 7.8 billion as on April 2020. China is achieved the first position with yearly change of 0.59% and India is in the second position with yearly change of 0.99%. It is predicted to reach 19 billion by 2050. Sixty one percent of the total population lives in Asia (4.7 billion), 17% in Africa (1.3 billion) and 10% in Europe and rest in other areas. The growth of human population affects the biodiversity which is essential for the healthy functioning of planets and ecosystem. Population is recognised as an indirect driver of biodiversity loss, as human demands for resources like food and fuel play key role in driving biodiversity degradation This happens primarily through the conversion of ecosystems to food production. More and more land is converted for agricultural use due to the increase of residential areas both in the urban and rural areas for more food production leading to the degradation of ecosystems and biodiversity. Thus the loss of habitat of plant and animal and overexploitation of natural resources along with the high population growth of human including urbanisation are the major cause of very rapid loss of biodiversity.

Humans actually use the natural resources of the earth to a maximum extent to meet their increased need from the resources of the planet without thinking about the need of other species of animal, insects etc. throwing other species to risk for their survival. The exploitation of land-use and habitat loss of wild life through human activity has resulted in making many animals and plants as endangered or extinct. The outbreak of COVID-19 has given us a great warning to remind us that human, animal, plant and environmental health are all intrinsically connected and it is the responsibility of highly evolved human being to restore and conserve biodiversity and health of the environment of the planet. Thus the recommendations will be to prevent the occurrence of future pandemic are to stop i) destroying nature ii) wild life trade iii) wild life consumption iv) high rate of human population growth.

For the cure of future pandemic of viruses we can recall one old advice of Benjamin Franklin in 1736 that “An ounce of prevention is worth a pound of cure.”

### iii) Vaccines

More than 90 vaccines are being developed against SARS-CoV-2 by research teams in companies and universities across the world but requires more human trial to come to the market. Researchers are trialing different technologies, some of which haven’t been used in a licensed vaccine before. At least six groups have already begun injecting formulations into volunteers in safety trials; others have started testing in animals. A COVID-19 vaccine developed in the University of Oxford and tested on a human for the first time on 16 April 2020 now awaits a comprehensive efficacy trial by mid-August before the race begins for Britain to find potential partners to manufacture the billions of doses the world needs. Scientific workers are trying with the following types of vaccine for combating the disease:

- Altimmune’s intranasal coronavirus vaccine (Gaithersburg, Maryland, USA)
- INO-4800 by Inovio Pharmaceuticals, USA
- mRNA-1273 vaccine by Moderna (Cambridge, Massachusetts, USA)
- Avian Coronavirus Infectious Bronchitis Virus (IBV) vaccine by MIGAL (ISRAEL)
- ‘ChAdOx1 nCoV-19 Vaccine developed from Oxford University (UK) and many more

However, all vaccines are in the developing stage only.
References

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11. Reports from SCIENCE Journal, April, 2020

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Corona-virus infections are generally mild in healthy adults, obviating any urgent need to develop treatments or vaccines. The replication cycle can be blocked at several stages using single or combined treatment paradigms: virus entry can be inhibited by antispike antibodies elicited by vaccines to block attachment or by preventing fusion using relevant protease inhibitors. RTC formation and transcription-replication events can be targeted using viral protease inhibitors or nucleoside analogues (GS-5734 or EIDD-1931). Interferon (IFN) sory proteins of SARS-CoV-2 and those of its closest human pathogen relative, SARS-CoV. Coronaviruses (CoV) were identified as human pathogens in the 1960s. They are enveloped positive stranded RNA viruses in the order of Nidovirales (Figure) [1]. With their characteristic surface, the virions have a crown-like appearance under the electron microscope, which is why the viruses are named after the Latin word corona, meaning crown or halo. Most coronaviruses infect animals (i.e. bats, birds and mammals) which act as an intermediate host reservoir. Coronavirus may have originated in bats or pangolins. The first known cases of COVID-19 were in Wuhan, China. Learn more about its origin, causes, and transmission here.