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Zoonotic Epidemics of Coronaviruses, Emergence of Covid-19, and Future Perspective for Zoonotic Diseases

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Abstract: Infectious emerging and re-emerging zoonotic epidemics are of greater threat for public health. Coronaviruses are group of related viruses that are mainly considered to cause diseases in mammals, birds and humans. During last two decades, it spilled over three times by zoonotic pathways with genetic modification and emerged as severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), middle-east respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In December 2019, pneumonia of unknown origin currently known as COVID-19 was reported which is linked to the wet market of Wuhan, China, has drained the attention of the world as global pandemic with 34,495,176 cases, 1,025,729 deaths from all territories of world (WHO, Weekly Epidemiological Update 2 October 2020). Complete genomic sequencing and phylogenetic studies revealed that SARS-CoV-2, a beta coronavirus, originated from bats with remaining codons of an intermediate host, which is still under research. SARS-CoV-2 is highly pathogenic and human to human spread makes it more virulent. Government institutions and private organizations have boosted the research for drug, vaccine and immunoglobulin development which are now under clinical trial phases. AI helped a lot in this panic situation and advancement in such technologies can help in combating such baffling battles. Therefore, collaborative world response and investment to reinforce research for technological advancements and strategically development in various disciplines to control future pandemics is perquisite.

Keywords: Global Pandemic, COVID-19, SARS-CoV-1, MERS-CoV, Zoonotic epidemics

Introduction

Emerging and re-emerging zoonotic outbreaks are a significant threat to public health like Hantavirus pulmonary syndrome, Henipa and Ebola viral diseases. Coronaviruses are positive sense, single stranded enveloped large RNA molecule with a molecular weight ranging between 29 to 32 kilobases virus having crown-like spikes and broad distribution in humans, mammals, and birds, causing respiratory, neurological, and enteric diseases (Lai et al., 2007). Since the first zoonotic emergence of Severe Acute Respiratory Syndrome (SARS-CoV-1) in 2002, coronaviruses have become a global public threat (Zhong et al., 2003). The continued evolution resulted in a second zoonotic epidemic, Middle East Respiratory Syndrome (MARS-CoV), in 2012, which caused a high fatality and gained the world's attention (Zaki et al., 2012). Given the wider distribution and prevalence, recombination of genetic material, an adaptation of new host through evolution, cross-species

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transmission makes the coronavirus emerge periodically with fatal outbreaks (Zhu et al., 2020). At present, the world is concerned about the third major zoonotic epidemic of a newly emerged coronavirus disease.

At the end of December 2019, pneumonia of unknown origin was reported which is linked to the wet market of Wuhan, China (P. Zhou et al., 2020). The epidemiological and etiological investigation was done on 31 December 2019 by the Center for Disease Control (CDC). Similar to other CoVs, the newly emerged novel coronavirus also affected the respiratory system, and clinical investigation of the affected patients showed symptoms of fever, cough, and rarely gastrointestinal infection (Guo et al., 2020; Kim et al., 2020). The genetic sequencing of the sampled virus revealed the novel coronavirus, an etiological microbe for the unknown disease. Phylogenetic studies showed that this is a different virus from SARS and MERS CoVs, originated from bats with an intermediate host, which is still unknown (Lu et al., 2020; P. Zhou et al., 2020; Zhu et al., 2020). World Health Organization (WHO) named SARS-CoV-2 to this newly emerged novel coronavirus and COVID-19 to the disease caused by this virus. Due to a large number of cases and wide spreading of conditions across the countries, on 30 January 2020, WHO declared COVID-19 a public health emergency of international concern. SARS-CoV-2 is highly pathogenic, with 34,495,176 cases, 1,025,729 deaths from all territories of the world (Weekly Operational Update 2 Oct, 2020). Further epidemiological surveillance, phylogenetic studies, medicine for treatment and active and passive immunization strategies for control are under investigation.

This review is focused on present insight of zoonotic epidemics caused by coronaviruses, their structure, phylogenetic origin, organization, and divergence of SARS-CoV-2 genome and to summaries the epidemiology, pathogenesis, clinical features of the COVID-19 along with prevention strategies to combat the disease on the bases of advances in previous research, with the aim to provide the brief recent research progress that will be helpful for epidemiologist, biologist and clinicians for disease investigation, drug and biologics development, and future planning for control of zoonotic epidemics.

Coronavirus Taxonomy

Nidovirales order contains three families of RNA viruses, including Roniviridae, Arteriviridae, and Coronaviridae (Figure 1). Coronaviridae is subdivided into two subfamilies, Torovirinae and coronavirinae respectively. Torovirinae mainly affects gastrointestinal tract of goats, pigs, horses, cats, and cattle. Up till now, this subfamily is not involved in infections, disturbing human health as they don’t have zoonotic propagation (Burrell et al., 2016). Coronavirinae is further subdivided in to four genera. Alpha-CoV infects humans and animals, Beta-CoV infects humans like severe acute respiratory syndrome corona virus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV) and animals, Gamma-CoV infects birds and whales, and Delta-CoV infects birds and pigs. Hibecovirus, Sarbecovirus, Embecovirus, Nobecovirus and Merbecovirus are subgenera of Beta-CoV (Cui et al., 2019). The CoV affects the respiratory system and mainly infect bats, dogs, mice, cattle and birds (Perlman and Netland, 2009). Saif (2004) reported that during the 20-century coronavirus was considered to cause only a minor respiratory disorder like 229E, NL63, HKU1 and OC43. In 21th century the old concept about the coronavirus changed entirely after the SARS-CoV attack in china (Peiris et al., 2003a) and the MERS-CoV report in Saudi Arabia (Zaki et al., 2012). To et al. (2013) stated that almost all coronaviruses are transmitted through animal (zoonotic).

Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-Cov-1)

The SARS was transmitted through close contact and droplets being produced during cough. It was a febrile syndrome that mainly affects the respiratory system leading to pneumonia. In November 2002, it was the first time reported in the Chinese province Guangdong (Woodhead et al., 2003). Later in 2003 February, it spreads to Hong Kong and five continents infecting approximately 30 other countries (Control and Prevention, 2003). Peiris et al. (2003b) stated that SARS-CoV spread as epidemically affecting 8000 people out of which 774 people died. The etiological agent for SARS was isolated and named novel coronavirus (SARS-CoV), categorized as Beta-coronavirus (Drosten et al., 2003; Ksiazek et al., 2003). The case fatality rate (CFR) proposed during the SARS-CoV outbreak was 9.6% (Leung et al., 2004). The significant sign appears in humans during severe condition is acute respiratory distress syndrome, its proportion is 16% but it increases the CFR from 9.6% to 50% (Fowler et al., 2003; Lew et al., 2003). Masked palm civet was considered the reservoirs of SARS 2003 and 2004 epidemics from zoonotic point of view (Guan et al., 2003; Kan et al., 2005; Song et al., 2005). Bats, belonging to mammalian family are also considered as reservoir of SARS-CoV (Figure 2) as it is also involved in many virus transmissions in last 20 years like Nipah, Rabies, Ebola, Hendra and

Menangle (Leroy et al., 2005; Mackenzie et al., 2001). Shi and Hu (2008) stated that SARS-CoV mainly found in Horseshoe bats but civet cats are carrier host of the virus. It can be transmitted zoonotically to humans and can cause massive pathogenicity.

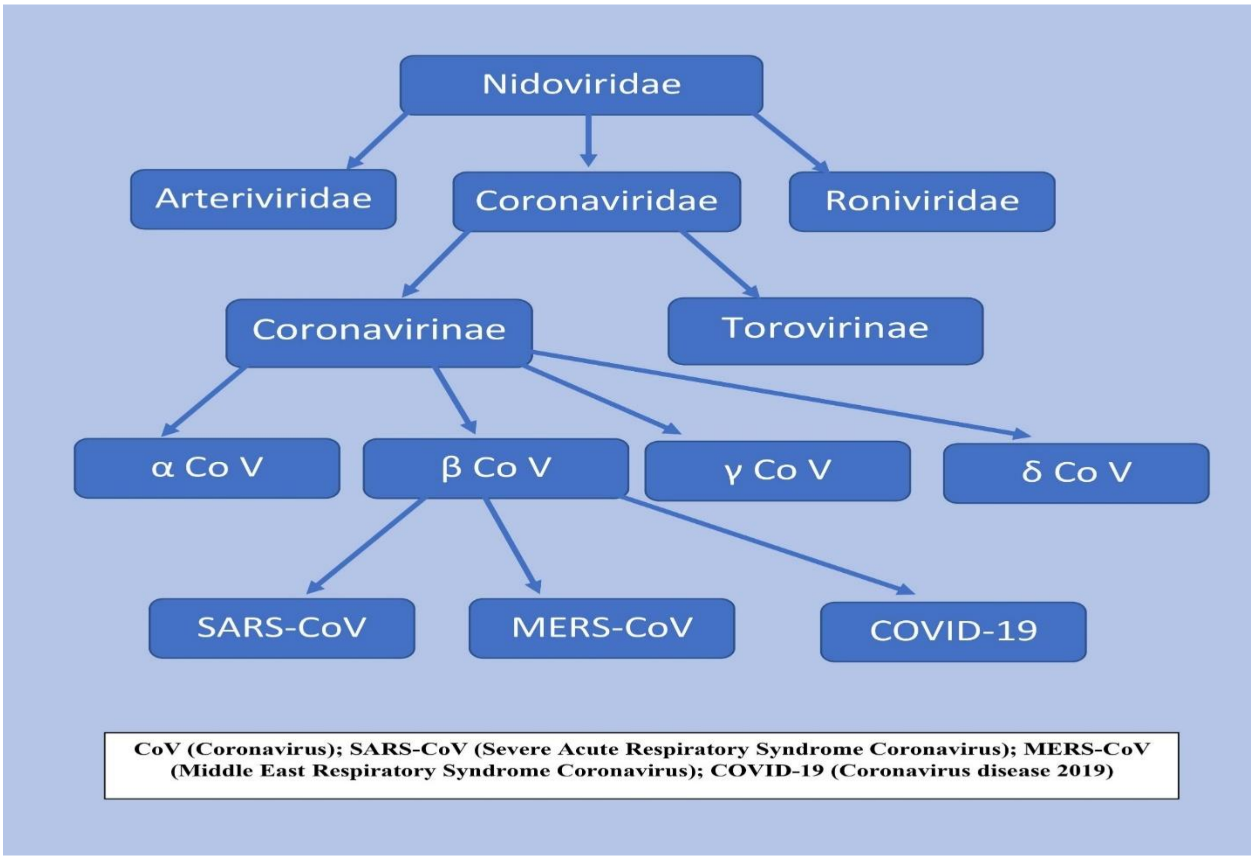

Figure 1. Flow chart diagram of Nidoviridae

Middle East Respiratory Syndrome Coronavirus (MERS-Cov)

In June 2012, MERS-CoV was firstly reported in Saudi Arabia (Zaki et al., 2012). Earlier, author named it as human coronavirus, but the International Committee on Taxonomy of Viruses later named it as MERS-CoV (Murphy et al., 2012). It was ranked as second coronavirus zoonotic disease propagating through bats to humans (Sharif-Yakan and Kanj, 2014). The first infected person was died due to respiratory disorder leading to renal failure. The MERS-CoV was genetically studied and found to be most similar to bat CoV (Cui et al., 2019). The total no. of infected people in 27 countries with MERS-CoV was reported as 2468 in December 2019 (Baharoon and Memish, 2019) with a mortality rate of 36% (Arabi et al., 2017). The later authors stated that most recently 186 new cases reported in South Korea, out of which 35 died. About 80% of all infected people with MERS-CoV belongs to Saudi Arabia. Camel was considered as a reservoir of MERS-CoV (Figure 2) but the genetic sequence matches with bat virus (Corman et al., 2014; Omrani et al., 2015; Sabir et al., 2016). Generally human contact with bats is rear, but camels are in constant contact with humans since ancient times. MERS-CoV transferred to camels from bats and spread to Africa and middle east territories rich with camel population (Hemida et al., 2014). Transmission of MERS-CoV to humans from camels has been reported in Africa, the Arabian Peninsula and Pakistan (Memish et al., 2014; Omrani et al., 2015; Zheng et al., 2019). The coronavirus strain isolated from camels and humans are genetically as well as phonetically identical (Farag et al., 2015). For diagnosis of infection sample from throat swab tested at nucleic acid level, but chest image and symptoms help in clinical diagnosis.

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2)

In the start of January 2020, rapidly propagating human pathogenic disease spreading zoonotically has been ranked third beta-CoV disease (Cui et al., 2019; Huang et al., 2020). The novel 2019 CoV noted as 2019nCoV resembles with previous out breaks of SARS-CoV-1 and MERS-CoV having the same etiological agent beta-CoV with alterations (Rodriguez-Morales et al., 2020). The first case was reported in 12th of December, 2019 in china (F. Wu et al., 2020) in Hubei province Wuhan city, showing resembling signs with pneumonia named SARS-CoV-2 (Q. Li et al., 2020; Zhu et al., 2020). Within a few weeks, this infection spreads all over the world, crossing border of different countries from China (Giovanetti et al., 2020; Harries and Takarinda, 2020; Phan et al., 2020). The Chinese scientists and medial focal persons quickly studied the genomic sequence of virus and share it with world to warn them of the dangerous condition (F. Wu et al., 2020). P. Zhang et al. (2020) stated that SARS-Cov-2 genome sequence resembles with bats or having slight modification due to involvement of other mammals in wet market of China. Later on, it started spreading swiftly from human to human with super spreading phenomenon (Riou and Althaus, 2020).

Epidemiology

Novel Coronavirus pneumonia later called COVID-19 was first reported from China in December. Chinese scientist team sent an alert to WHO on 31 December 2019 regarding large no of cases showing signs of flu. Later on, the 5th of January, WHO has press released to warn the world to stop travel movement from China to other countries. This unknown agent causing a large no of infection throughout the public was identified as 2019 novel coronavirus (2019nCoV) on the 7th of January. The cruelty of this virus was showed in front of all world after first death due to 2019nCoV on 11th of January. After this kind of response, first committee on this emergency condition was organized by WHO to tackle and investigate this 2019nCoV on 22th of January. Later on, it spreads rapidly all over the world across border affecting all regions of the world. It was declared as a pandemic by WHO on 11 March, 2020 (Organization, Situation Report – 51, 2020). According to the latest update of WHO 26 March 2020 report, COVID19 has been confirmed in 201 territories (Organization, Situation Report – 66, 2020). It was stated in COVID-19 report no. 59 that the first 10000 cases take round about three months, but the next 100000 cases only take 12 days (Organization, Situation Report – 59, 2020). This swiftly increasing pattern shows the pandemic outbreak of COVID-19. To take a better step for the prevention of such kind of pandemic disease accurate database regarding laboratory data, epidemiological figures, and the clinical records should be provided (Morgan, 2019). Jin et al. (2020) reported that people with older age are more prone to COVID-19, whereas there is no gender discrimination for COVID-19 susceptibility. The later author further stated that female patients are less prone to COVID-19 irrespective of age. The CFR of patients older than 80 years was 14.8% as compared to 40-49 years patients having 0.4% in China (Gao et al., 2020). The ISS (2020) stated that CFR on 13, March in Italy was 21.1% in the age group of more than 90, 17.5% in the age group of 80-89, 10.8% in the age group of 70-79 and 6% for less than 50 years of age. According to CDC report 2.3% was overall Case Fertility Rate (CFR), cases with 70-79 years of age had 8.0% CFR and cases with 80 years of age and older had 14.8% CFR but no death was reported among group of 9 years old and younger ones (Surveillances, 2020). Critical cases had 49.0% CFR while mild and severe cases had no death (P. Wu et al., 2020). The later authors reported that among patients with previous comorbid conditions CFR was raised as following, 6.3% for chronic respiratory diseases, 10.5% for cardiovascular disease, 5.6% for cancer, 7.3% for diabetes and 6.0% for hypertension.

Nioi and Napoli (2020) conducted a trial on malaria and COVID-19 paradox epidemiology. The later authors concluded that under developed countries, which under goes malarial threat in history are less prone to COVID-19 as compared to developed countries. The possible reason for such kind of trend can be linked with treatment of malaria with anti-malarial drugs against virus, leads to development of immunity against viral attacks. To update public regarding latest updates on COVID-19, WHO has launched a service with collaboration with Facebook and WhatsApp. To utilize this portal just send a “Hi” message on +41 798931892 and the user will receive recent updates regarding COVID-19 as well as precautionary measures. Solidarity Trial study plan has been launched by WHO to find more suitable treatment plan with collaboration of keenly working organization on COVID-19.

Phylogenetic Origin of SARS-Cov-2

The epidemic existence of the COVID-19 is not mosaic. The evolution of the virus has a relation to the sea market of Wuhan, China, and this sea market might be the critical reservoir of SARS-CoV-2 (Giovanetti et al., 2020). But still, there is no evidential existence relating to the origin of SARS-CoV-2 to the sea market. Recent complete evolutionary researches refer bat to be an ancestor host of SARS-CoV-2 (Ashour et al., 2020; Lake, 2020; Phan, 2020; P. Zhou et al., 2020). But there is evidence that bats were not being sold in the market, and only 1.18%of patients had exposure to wildlife (Z. Liu et al., 2020; P. Zhou et al., 2020). Complete genomic sequence interpretation of the SARS-CoV-2 with pangolin and human as host showed higher similarity than rhinolophine and human as host. Pangolin genomic sequences are not just similar but also homologous to SARS-CoV-2. Phylogenetic analysis of the data reveals the similarity of receptors residues from different species like snakes, rabbits and turtles that might be the intermediate host in the emergence of the newly discovered coronavirus (figure 2) (Z. Liu et al., 2020). SARS-CoV-2 is significantly congregated with bat SARS-CoV and different from SARS-CoV-1 (Benvenuto et al., 2020). Recombination in the S glycoprotein of SARS-CoV-2 on the bases of bias usage of codon suggests cross-species transfer from snake as compared to other species (Ji et al., 2020). But some recent studies omitted the snake as an intermediate host of SARS-CoV-2. Further studies are still required to investigate intermediate host responsible for viral transfer from bats to humans. Genomic sequencing of SARS-CoV-2 revealed similarity ranges from 55.6% to 56.1% to the other flu viruses, which shows that they are totally different from SARS-CoV-2. For understanding the genomic similarity between previous human host zoonotic CoVs like SARS and MERS, researchers studied the complete genomics of these CoVs. The SARS genome showed a similarity of 82.6%, which was also higher than the similarity of MERS CoV (Guo et al., 2020; Kim et al., 2020). The Phylogenetic tree of SARS-CoV-2 and other beta CoVs, is shown in figure 3. Sequence Identity results of Lu shows 88%, 79% and 50% identity to bat SARS, SARS and MERS COVs respectively, which is lower than the other studies that might be due to the usage of different strains genomic analysis which has undergone a little mutation (Lu et al., 2020). Computational Complete genomic analysis of environmental and body SARS-CoV-2 are homologous with the highest similarity of 99.7%. Twenty-one strains from various countries are homologous and share the same origin that is not astounding because of global traveling (Li et al., 2020). TheSARS-CoV-2 strains from various countries undergo small mutation but are highly similar to each other. Tang classified the SARS-CoV-2 into L and S type based on the population genetic evaluation of SARS-

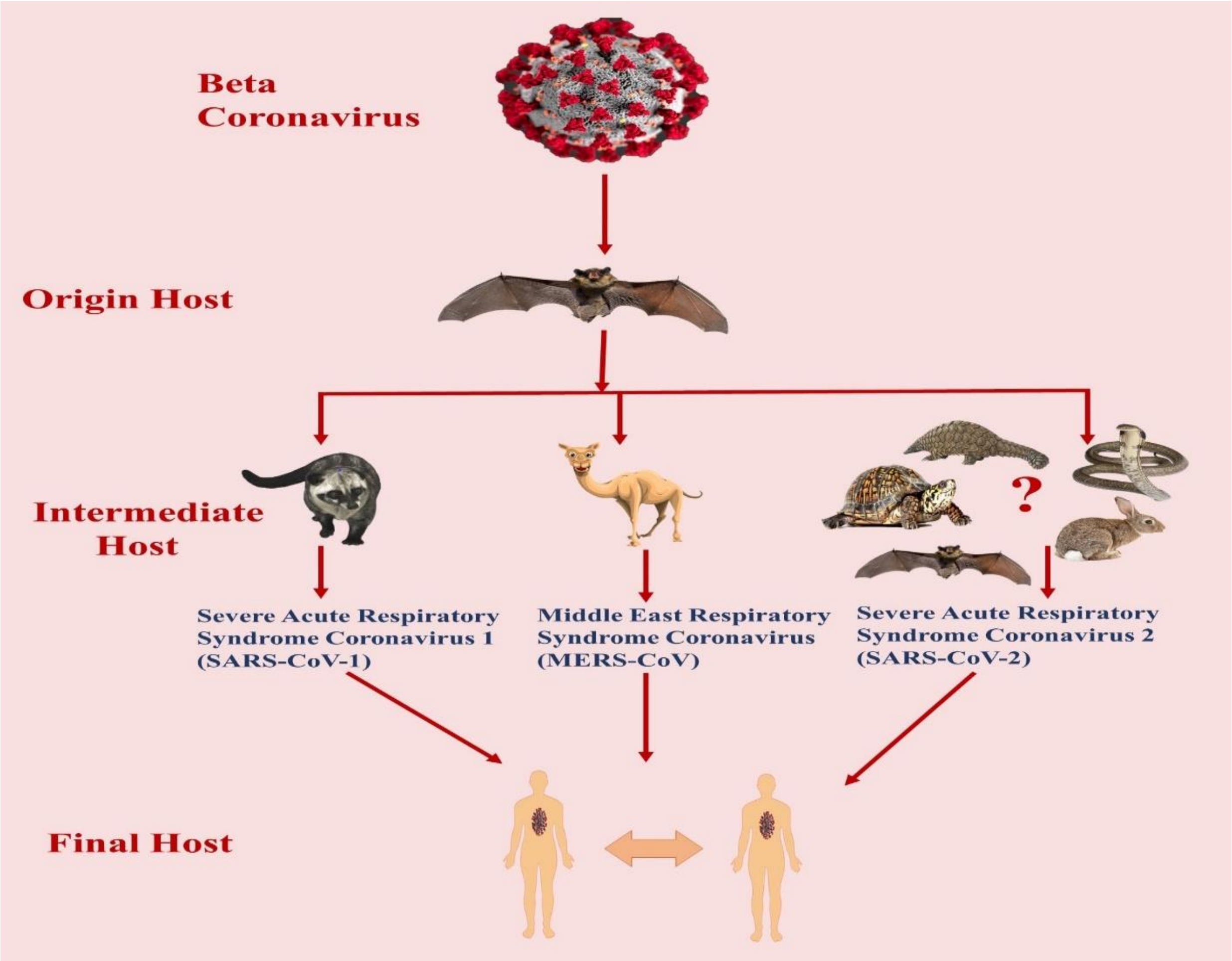

Figure 2. Schematic diagram showing origin of recent zoonotic epidemics from Beta Coronavirus: a serious health threat

CoV-2 (Tang et al., 2020). The L type is emerged from the S type and is more contagious. Epidemiologists are required to practically observe and study the virulence and transmission of both types.

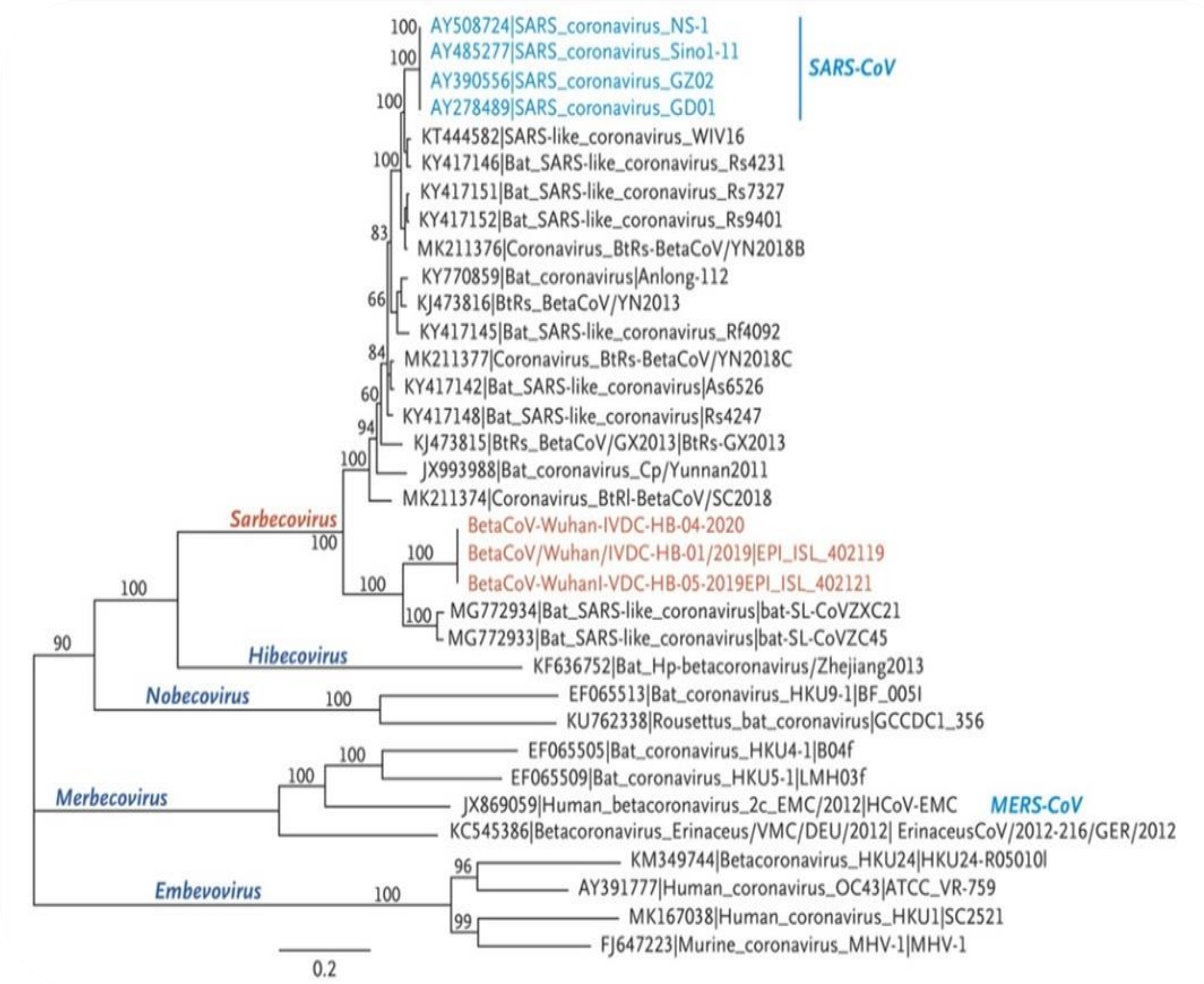

Figure 3. Phylogenetic origin tree between SARS-CoV-2 and other beta corona viruses (Zhou *et al*., 2020)

General Morphology of SARS-CoV-2

SARS-Cov-2 is a spherical, positive sense, single-stranded enveloped RNA virus having crown-like projecting spike proteins from the surface of virion which are also characteristic structure of other CoVs (figure 4). The particle size of the virus ranges from 70 to 90 nm (Kim et al., 2020). The Viral structure is composed of nucleocapsid proteins (N) and structural proteins comprising of an envelope (E), spikes(S) and membrane (M) proteins. The structural and the nucleocapsid proteins are associated with their specific functions. During assembly of RNA into particles N protein interacts with viral RNA (Chang et al., 2006). The S protein comprised of S1 and S2 subunits are highly glycosylated protein that aids for entry of the virus into host cells (Siu et al., 2008). Abundant amount of the M protein in the virus is responsible for giving shape to the virus. The E protein is involved in mature envelope development during the assembly process of the virus.

SARS-CoV-2 Genomic Organization and diversification

SARS-CoV-2 like the other beta coronaviruses shares the similar genomic structure constitute of 5′ and 3′ un-translated regions, six Open–Reading–Frames (ORFs), S (spike), M (membrane), E (envelope) and N (nucleocapsid) genes as shown in figure 5 (Cui et al., 2019; Phan, 2020; P. Zhou et al., 2020). Zhang analysis revealed mutation in viral genome isolated from different pneumonic patients in China (L. Zhang et al., 2020).

Complete genomic analysis showed deletion in genome isolated from Australia, Japan, and America (Phan, 2020). The mutation degree in the SARS-CoV-2 genome was lower as compared to mutation diversity in the avian influenza virus (H7N9) (Wu et al., 2015). Open –Reading –Frames (ORF1ab) polyproteins showed two deletions at three and twenty-four nucleotides and one deletion at 3′end genome. The entire genomic sequence of the SARS-CoV-2 revealed 93 mutations and except E protein, 42 mutations are recognized at structural and non-structural proteins. In ORF1ab polyproteins, S protein, N protein, and M protein twenty-nine, eight, four and one mis-sense mutations are identified. On N region at 380th and 410th amino-acidic position Glutamine is replaced by Asparagine and Threonine residue is replaced by Alanine respectively in viral genome isolated from a pneumonia patient at Wuhan, China. Asparagine residue is replaced by Glutamine and Alanine residue is replaced by Threonine at 409th and 380th amino-acidic positions respectively at clade-II of SARS-CoV-2 strain isolated in Wuhan. Asparagine residue replaced the Aspartic residue and Threonine residue replaced the Alanine residue at 536th and 644th amino-acidic position on S region of Wuhan strain of SARS-CoV-2. At 380th and 309th amino-acidic position SARS-CoV-2 and bat CoV share identical amino-acidic sequence which is different in SARS-CoV-1. S protein amino-acidic sequence of SARS-CoV-2, bat CoV and SARS-CoV-1 at 536th and 644th amino-acidic position is different in all three types of these viruses (Benvenuto et al., 2020).

Conserved classification replicase domains amino acid sequences at ORF1ab among SARS-CoV-1 and SARS-CoV- 2 are 94.4% identical, showing both viruses from same specie origin (P. Zhou et al., 2020). Paraskevis et al. (2020) rejected the emergence theory of SARS-CoV-2 through recombination of the previous COVs and proposed that SARS-CoV-2 come into existence through clustering of bat-SARS-CoV genome. Lu et al. (2020) demonstrated that E gene has highest similarity (98.7%) with two bat- SARS – like CoVs at 13 regions. But codon base analyses of S proteins suggest that SARS-CoV-2 might the result of recombination originated from the coronavirus which is still unknown and un-sampled (Ji et al., 2020). SARS-CoV-2 has higher percentage of pyrimidine than purines. Lower effective numbers of codons make SARS-CoV-2 higher codon bias and highly gene expressive than SARS-CoV-1 and MERS (Kandeel et al., 2020). The addition of the several glycoproteins encodings, adding properties of hemagglutination and acetyl esterase in SARS-CoV-2, make it different from other related beta coronaviruses (Wu and McGoogan, 2020). The S protein is disparate from other SARS-CoVs with nucleotide similarity less than 70%. Furthermore, S gene of SARS-CoV-2 is also larger than SARS-CoV-1. Three insertions at N-terminal of S gene and four key remains in receptor–binding motif divaricate the SARS-CoV-2 spike genomic sequence from other SARS-CoVs spike genomic sequence. Spike protein is responsible for virus host interaction and main target for neutralizing antibodies (Fung and Liu, 2019; Yu et al., 2020). Any alteration in this protein can change the antigenicity and host tropism of the virus. Still no detailed information in the amino acid configuration of the S proteins is not available that must be investigated.

Preventive measures for such zoonotic outbreaks in the future

Genetic spillover of viruses with the passage of time and rapid spread to a massive number of populations is a problem of the hour. Marvelous struggle of the scientists and the governments resulted in reduction in the severity of the outbreak in some countries but some countries are still under big threat. Scientists are working continually in order to control the present situation. A great millstone has been covered with studying the virus, testing drugs and biologics which are under clinical trials. But still there is a gap at molecular level in the origin, cross-species transmission, mutation, pathogenicity, early screening of the suffering patients and epidemiological spread. Re-emergence of the more virulent coronavirus from animals to human is the indication for the future threats to public health. It is therefore recommended to ban legal or illegal farming of wildlife and their trade should also be banned anywhere in the world except Zoo and Safari Parks. To tackle such kinds of infectious epidemic issues in the future, it is highly recommended to test out virus profiles of all the wild animal species encounter directly or indirectly with the human. In-vitro experiments of genetic modification of these viruses and their outcomes with effective treatment and control should be proposed projects for well-established genomic labs. There should be a global backup for such kind of new information under the supervision of the World Health Organization. General public awareness courses should be launched to educate people to handle such type of emergency.

The learned lesson from this outbreak is if a new virus outbreak occurs in any country than all countries should make the risk analysis on emergency basis for prevention and control. National disaster authorities with epidemiologists from medical and veterinary sciences (One Health) interlinking with information technologist can speed up innovation and technology for current and upcoming possible disasters. Surveillance among wildlife to identify the high-risk pathogens they carry and among people who have contact with wildlife to identify early spillover events is the time need. Improvement of market bio security regarding the wildlife trade is an essential component for prevention of emerging zoonotic outbreaks. Priority should be given to the research regarding future prevention of such outbreaks and transmission of zoonotic diseases. The future of such zoonotic outbreaks is not just dependent on the mutation and re-emergence of pathogens but also based on the strategies, measures and technologies we develop for the future of public health.

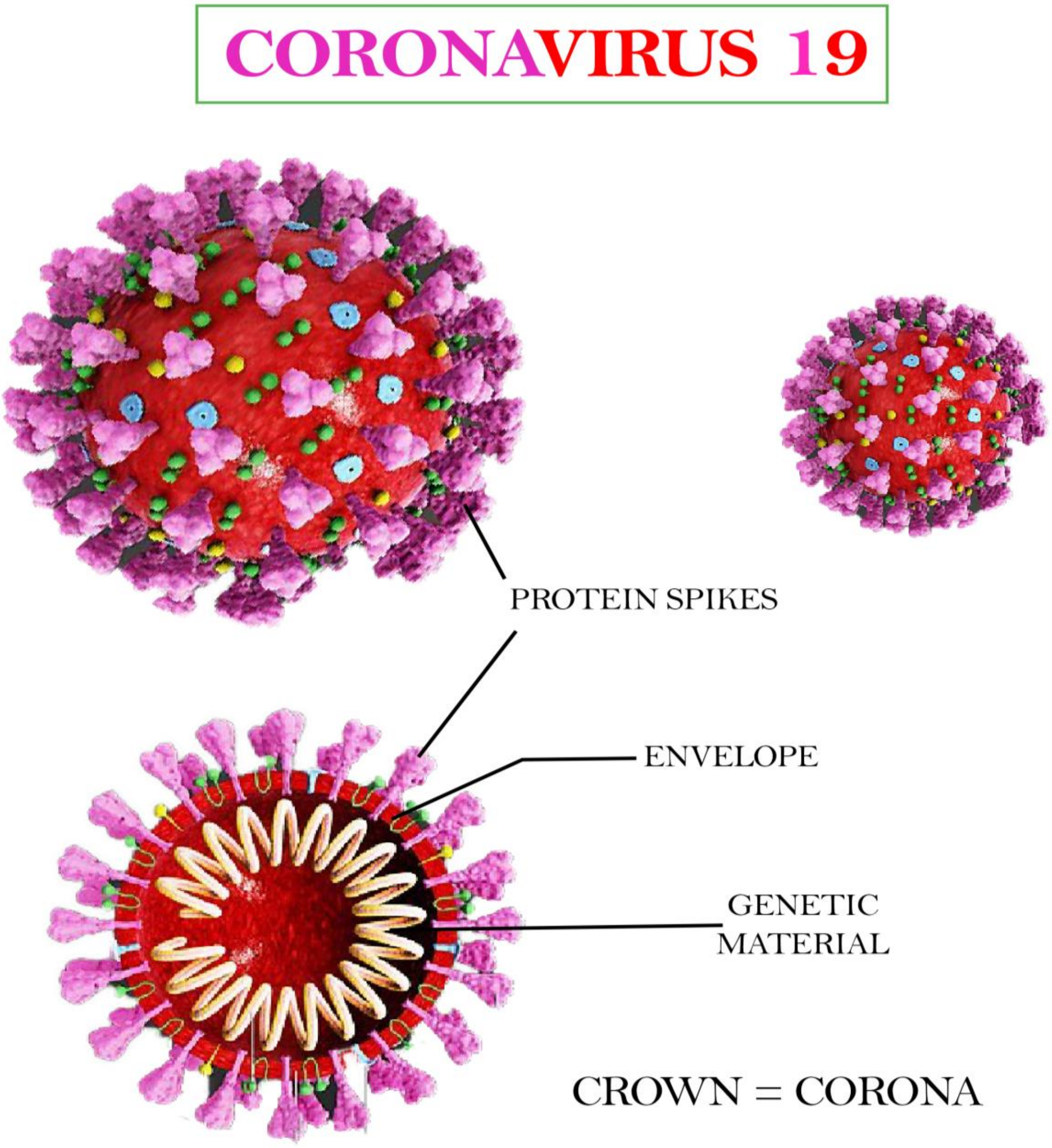

Figure 4. Illustration showing general structure of the newly emerged corona virus SARS-CoV-2

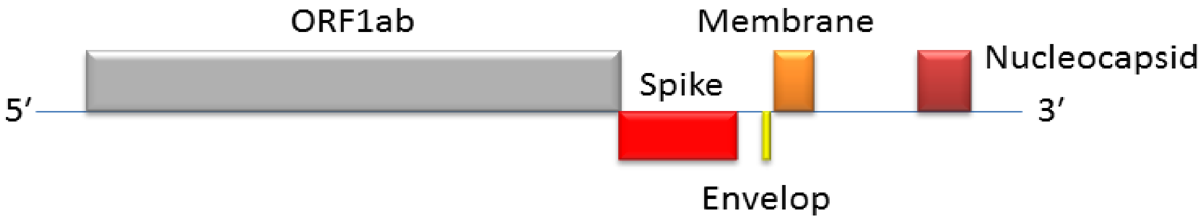

Figure 5. SARS-CoV-2 genomic arrangement demonstrating 5′ and 3′ ends, and various structural

Conclusion

Zoonotic diseases outbreak from coronavirus is still a matter of concern, as it spilled over 3rd time from the wild. In December 2019, COVID-19, has drained the attention of the world. SARS CoV-2 the responsible etiological agent enters to host cell by binding to ACE2 of the host cell and leads to multiple organ failure with most obvious respiratory symptoms (coughing, sneezing, shortness of breath and fever). SARS-CoV-2 most likely has a zoonotic origin (mammals). We should have to focus on three areas specifically to control and prevent such further epidemics and pandemics as following; Monitoring of wildlife animals to identify if they carry any dangerous pathogens, monitoring of people in contact with wildlife animals to diagnose early spillover of disease and biosecurity of wildlife markets should be improved to control and prevent pathogens related to wildlife animals.

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