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COVID-19 Pandemic: The Origin, Transmission, Pathogenesis, and Therapeutic Application

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ABSTRACT

An outbreak of atypical pneumonia reported in late December 2019, which subsequently progressed to global health crises of significant magnitude within the first three months after its appearance and the etiology was traced to a seafood wholesale market in the city of Wuhan, China. Where a large number of infected patients are presumed to have been exposed to the wet animal market and this was the first confirmed incident recorded. The genome sequence of this unknown pathogen was obtained and then through carefully genome sequence comparison with the already previously characterized corona viruses; SARS-CoV and MERS-CoV, it was found that a betacoronavirus belonging to subfamily orthocoronavirinie is responsible for the pneumonia cases. This suggested that Wuhan was the site where COVID-19 first started and the disease is zoonotic in origin. COVID-19 pandemic has presented considerable challenges to public health care systems at global scale and dictates almost every aspect of medical practice and policies across the world. Apparently, an effective treatment therapy against COVID-19 is the most urgently needed to curb the rapidly increasing incidence of SARS-CoV-2 infections. Unfortunately up to this moment there is no approved drug for the treatment of COVID-19 patients, although many reports are suggesting the drugs which were previously used against SARS-CoV and MERS-CoV such as remdesviri, lopinavir, ritonavir, interferon beta-1b, and ribavirin but these are being tested in randomized trials and again mostly showing less clinical benefits. Use of a triple combination of interferon beta-1b, lopinavir-ritonavir and ribavirin drugs were reported to be effective than when each drug is used separately, however, collaborative investigations are needed to ascertain the fidelity of these drugs. In this review, we summarize the latest research progress of the origin, pathogenesis, clinical characteristics of COVID-19, and discussed the current treatment regimens for combating the COVID-19 pandemic.

Keywords: SARS-CoV-2, COVID-19, Betacoronavirus, Therapeutics.

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1 INTRODUCTION

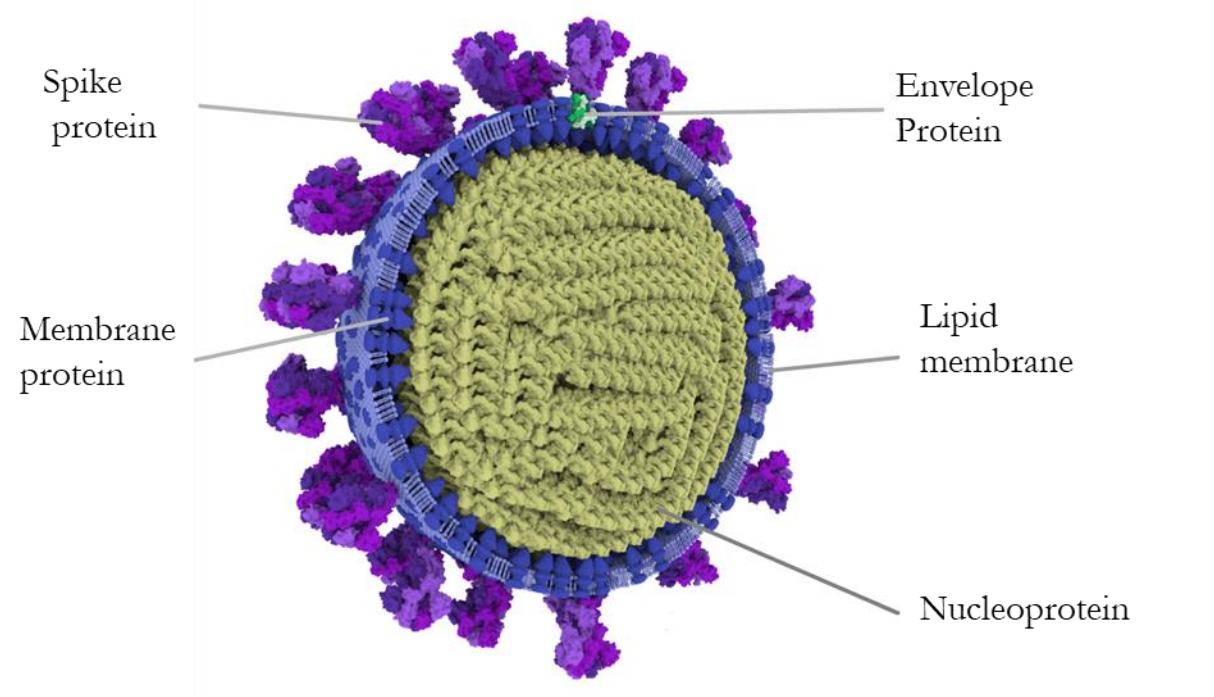
Severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2) is confirmed to be the causative agent of coronavirus disease -19 (COVID-19), that was first reported in late December 2019 in City of Wuhan, China [1]. The disease is presumed to be of zoonotic origin [2], that is manifested in acute pneumonia resulting to a respiratory failure, including death [3], [4], the symptomatic features of COVID-19 include fever, cough, and shortness of breath, which appears between 2 to 14 days after the initial exposure to the virus [5]. Owing to its high transmissibility between persons of all ages SARS-CoV-2 rapidly spread in unprecedented manner and engulfed the entire globe as a new pandemic [3], [4], [6], [7]. This subsequently overwhelmed the health care systems on global scale [8], [9], On February 11, 2020, the [11], [12], officially named the infection due to the virus as coronavirus disease 2019 (COVID-19) and on March 11, 2020 the [11], [12], declares COVID-19 as a pandemic. Since then SARS-CoV-2 has infected over 11 million people with more than 500,000 deaths as of 3rd July, 2020.

Generally, coronaviruses are enveloped positive sense single stranded (ssRNA) viruses they belong to order Nidovirales, family coronaviridiae, subfamily orthrocoronavirinae and they are classified under four genera, namely; Alpha coronavirus (αCoV), Beta coronavirus (βCoV), Gamma corona virus (γCoV), and Delta corona virus (δCoV) [13], [14]. Coronaviruses are known to infect humans, other mammals and birds, frequently causing respiratory, enteric, hepatic and neurological diseases [15], [16], they comprised of six species which are pathogenic to humans, of which four include; HKU1, NL63, OC43 and 229E causes common cold symptoms in immunocompetent individuals [17]. While the other two species are severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) which causes much more severe disease with fatality cases and both are zoonotic in origin [14], [18]. However, from evolutionary perspectives it was established that Alpha coronavirus (αCoV), and Beta coronavirus (βCoV) originated from bats and rodents, whereas Gamma corona virus (γCoV), and Delta corona virus (δCoV) were of avian origin [19]. Evidence revealed high degree of genome sequences similarity of SARS-CoV-2 with SARS-CoVs and MERS-CoVs [20], [21], furthermore, the phylogenetic analysis revealed that bats are the source of SARS-CoV-2 [22]. Other studies also suggested that the origin of SARS-CoV-2 is associated with pangolins [23], [24]. However, recent report revealed that domestic cats seems to be a silent intermediate host in the chain of transmission for SARS-CoV-2 [25], so more studies are needed in order to understand the characteristics, the hosts and the transmission chains of SARS-CoV-2 prior to winning the war against COVID -19 pandemic.

1.1 Morphology and Origin of SARS-CoV-2

Corona-viruses (CoVs) are spherical crown shaped and enveloped RNA viruses (Fig. 1), with genome sizes ranging from 26 to 32 kilo bases [17]. The SARS-CoV-2 particle consists of three structural proteins, namely; the spike (S), a structure vital in viral infection, envelope protein (E) and membrane protein (M) which formed the viral envelope, whereas nucleocapsid contain the non-segmented RNA genome [26], [27].

Following the outbreak of pneumonia cases in Wuhan, China, there was urgent need to establish the cause of this illness, and then subsequently it was found that sever acute respiratory syndrome coronavirus -2 (SARS-CoV-2) is responsible for the outbreak of this new disease [1]. Although there has been no consistent evidence of coronavirus reservoirs other than mammals and birds [20], but the best-known examples include severe acute respiratory syndrome CoV (SARS-CoV) which emerged in China in 2002-2003 [28], [29], [30], that caused a large-scale epidemic with about 8000 infections and 800 deaths, and Middle East respiratory syndrome CoV (MERS-CoV) which has caused a persistent epidemic in the Arabian Peninsula since 2012. In both of these epidemics, the two viruses are believed to have originated from bats [31], and then jumped into another amplification mammalian host for SARS-CoV and the dromedary camel (*Camelus dromedarius*) for MERS-CoV [32], before crossing species barriers to infect humans [33]. Through phylogenetic analyses of RNA–dependent RNA polymerase (RdRp) protein, spike protein and full length genome of SARS-CoV-2 with SARS-CoV and MERS-CoV, it was found that the new viral pathogen (SARS-CoV-2) is closely related to the two bat SARS-like coronaviruses, namely bat-ZL-CoVZXC21 and bat-SL-CoVZC45, which belong to Sarbecovirus of Betacoronavirus [20], [34], [35], [36], [37], also there is high degree of similarity with genome of bat coronavirus RaTG13 from Yunnan [38], [39]. On the other hand Pangolins (*Manis javanic*) are believed to be another intermediate host for coronaviruses [40], [41], although some reports are urging that SARS-CoV-2 is the recombinant virus from bat-CoVs and Pangolin -CoVs [42], in which this homologous recombinants triggered cross-species transmission, evolution and thrives for more adaptability [42]. Genome recombination of viruses occur when two different parent viruses co-infect the same host cell and interact during replication forming descendant viruses that possess genes from both parental viruses, recombination events has often been associated with the expansion of the host range, increase in virulence, the evasion of host immune system and the evolution of resistance to anti-viral drugs [43]. In addition, recently it has been reported that transmission of SARS-CoV-2 can occur between domestic cats, which raises another question whether domestic cats may be a silent intermediate host of SARS-CoV-2, [25]. However, SARS-CoV-2 is confirmed to have started in City of Wuhan, China [1], [2], but it is unknown how the SARS-CoV-2 of Wuhan got transmitted from bats to humans? Although pangolins have been suspected as intermediated host but again transmission of SARS-CoV-2 among the domestic cats also is another puzzle warranting more investigations. It should be understood that the recombinants have the potential to infect and survive in new hosts including humans which spread through contacts and also recombinants use this as a natural process for the viruses to increase genetic diversity.



Figur 1. Schematic representation of SARS-CoV-2; particle morphology indicating surface viral proteins; spike glycoproteins, viral membrane protein, nucleoprotein, and lipid membrane

1.2 SARS-CoV-2 Transmission chain

SARS-CoV-2 the causal agent of COVID-19 is highly transmittable and pathogenic [44], [45], previously it was known that SARS-CoV is transmitted from bats via an intermediate host [31], and then to humans, while MERS-CoV is transmissible from bats to camels and then to humans [32], [Fig. 2]. Several reports have suggested that person-to-person transmission is a likely route for spreading SARS-CoV-2 infection [5], [36], [45], [46], [47]. This is supported by cases that occurred within families and among people who did not visit the wet animal market in Wuhan [14]. Person-to-person transmission occurs primarily via direct contact or through droplets spread by coughing or sneezing from an infected individual (Fig. 2). Saliva can be emitted through cough and respiratory droplets even during normal breathing [36], investigations are required to delineate the sources of SARS-CoV-2 in saliva [48]. SARS-CoV-2 was isolated from fecal swabs and blood, indicating the possibility of multiple routes of transmission. But no evidence indicate that there is vertical transmission from mother to child so far, as most known cases involving pregnant mothers underwent caesarean sections, so it remains unclear whether transmission can occur during vaginal birth or not, is an open question for investigation. However, based on current epidemiological investigation, the incubation period is 1–14days, mostly 3–7 days, and the COVID-19 is contagious during the latency period [49], [45]. SARS-CoV-2 is highly transmissible in humans, and it appears to be more severe especially in the elderly and patients with underlying diseases such as hypertension, diabetes, cardiovascular disease, obesity [50]. Recently, SARS-CoV-2 transmission has been detected among the domestic cats, but it is not yet known whether

SARS-CoV-2 can be transmitted between humans and domestic cats. In addition, presence of SARS-CoV-2 among tigers and lions at the Bronx zoo have been reported, and this poses serious threat. Moreover, it is worth to note that transmission between domestic cats signaled another problem, because domestic cats may be another silent intermediate host of SARS-CoV-2, since it seems that cats do not show any recognizable symptoms [25].

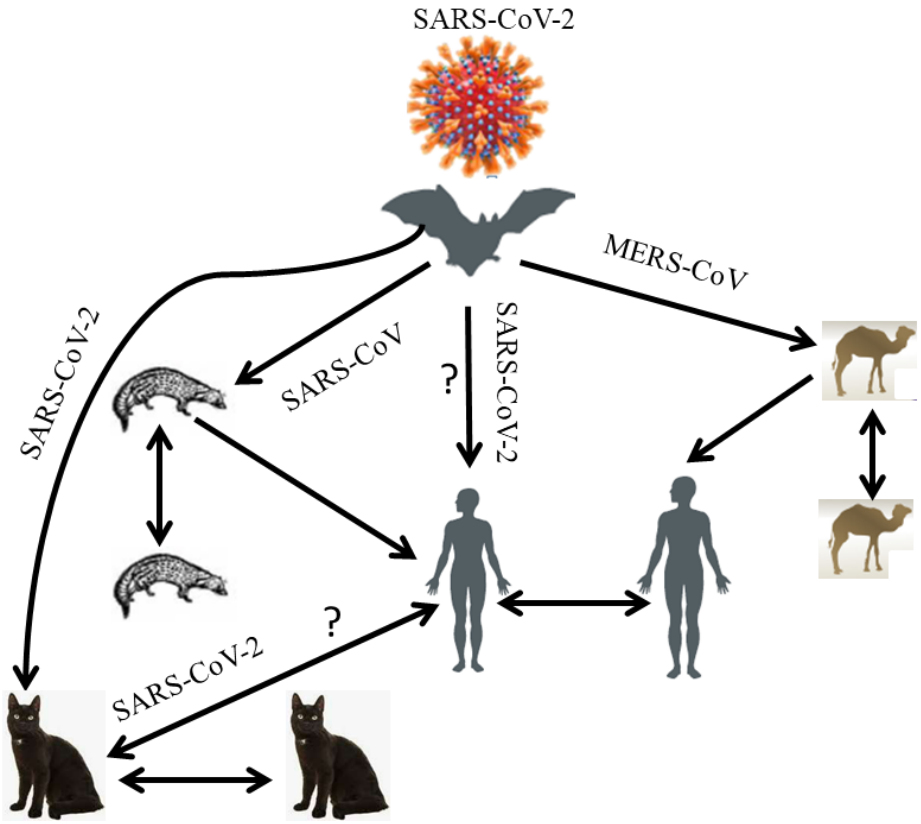


Figure 2. The illustrations represent the transmission chain of coronaviruses including; SARS-CoV, MERS-CoV, through an intermediate hosts pangolins and Camels respectively. However, SARS-CoV-2 transmission is presumed to follow the same trend from bats [23], via animals or intermediate host and then to humans, but its intermediate host(s) is/are not yet known, but Pangolins are suspected [24], [25]. SARS-CoV-2 has been also detected in domestic cats [26], which might be another potential intermediate host?

1.3 Genome organization

The single-stranded RNA genome of the 2019-nCoV is 29891 nucleotides in size, encoding 9860 amino acids. The G+C content was 38%, similar to other βCoVs, the 2019-nCoV genome contains two flanking untranslated regions (UTRs) and a single long open reading frame encoding a polyprotein. The 2019nCoV genome is arranged in the order of 5'-replicase (orf1/ab)-structural proteins [Spike (S)-Envelope (E) Membrane (M)-Nucleocapsid (N)] −3' and lacks the hemagglutinin-esterase gene which is characteristically found in lineage A β-CoVs (Figure 3).

1.4 Comparing SARS-CoV-2 genome structures to other Coronaviruses

Generally, the genome of coronaviruses ranges between 26 to 32 kb and consisting of 6 -11 open reading frames (ORF) encoding 9860 amino acids (aa) polyproteins [17], [51]. The genome of betacoronavirus comprises of; 5'-untranslated region (5'-UTR), open reading frame (orf) 1a/b (yellow box) encoding non-structural proteins (nsp) for replication, structural proteins including spike (blue box), envelop (orange box), membrane (red box), and nucleocapsid (cyan box) proteins, accessory proteins (purple boxes) such as orf 3,6,7a,7b,8 and 9b in the 2019-nCoV, (HKU-SZ-005b) genome, and the 3'-untranslated region (3'-UTR) Figure 3. Examples of lineages A to D betacoronaviruses include human coronavirus (HCoV) HKU1 (lineage A), 2019-nCoV (HKU-SZ-005b) and SARS-CoV (lineage B), MERS-CoV and Tylonycteris bat CoV HKU4 (lineage C), and Rousettus bat CoV HKU9 (lineage D) [52]. There are no significant differences observed between the genome of SARS-CoV-2 and the other SARS-CoV in terms of the ORF and non-structural proteins (nsps). However, SARS-CoV-2 lacks the hemagglutinin-esterase gene, but has two flanking untranslated regions (UTRs) at 5' end of 265 and 3' end of 358 nucleotide positions. The structure of spike glycoprotein (S) of SARS-CoV-2 comprised of S1 and S2 subunits which resembles the spike proteins of SARS-CoV with an RMSD of 3.8Å, but its receptor binding region (RBD) possesses highest divergence with 10-20 times highest affinity in comparison to other SARS-CoV [53]. In addition the S protein of SARS-CoV-2 is reported to have furin cleavage site (PRRARS'V) at the interface between S1 and S2 subunits that is processed during the biogenesis [54]. The S1 subunit contains a signal peptide, followed by an N-terminal domain (NTD) and receptor-binding domain (RBD), while the S2 subunit contains conserved fusion peptide (FP), heptad repeat (HR) 1 and 2, transmembrane domain (TM), and cytoplasmic domain (CP). S2 subunit of 2019nCoV is highly conserved and shares 99% identity with those of the two bats SARS-like CoVs (SL-CoV ZXC21 and ZC45) and human SARS-CoV [24], [55], Orf 8 is an accessory protein found Betacoronavirus lineage in the B coronaviruses [56].

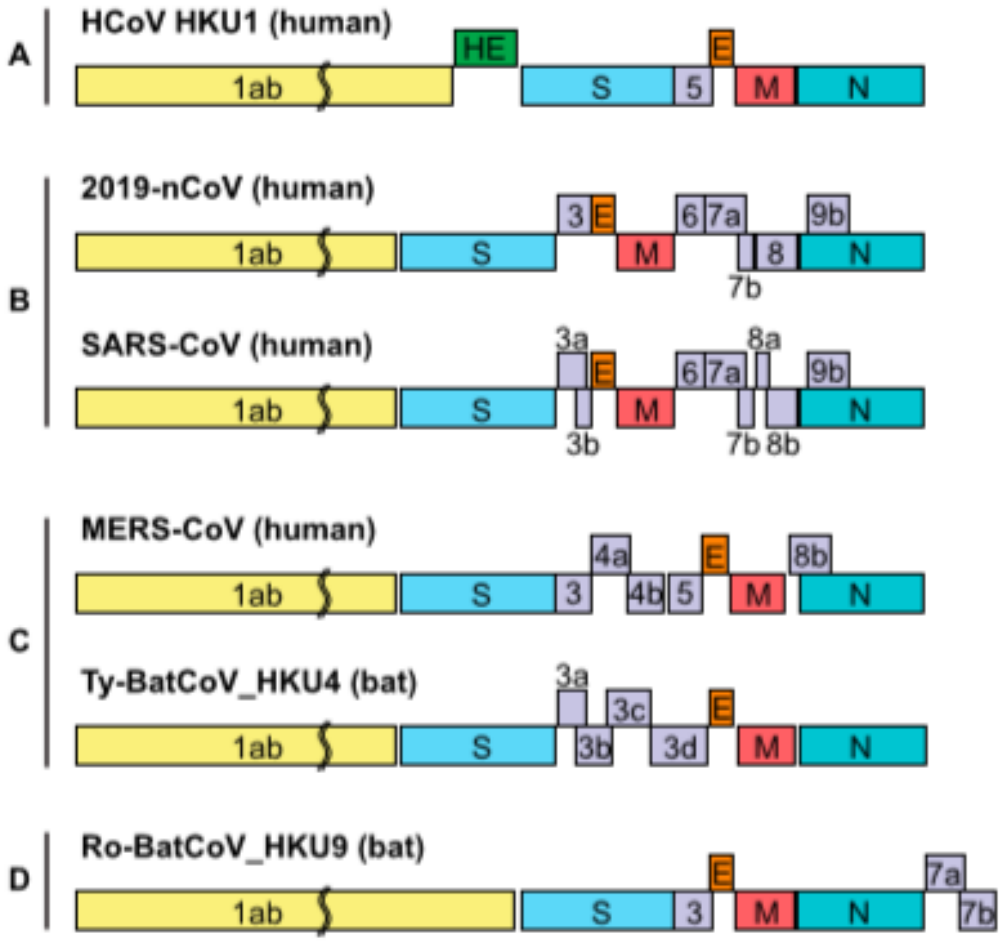


Figure 3: Schematic structure of Betacoronavirus genome organization representing five species; HCov HKU1 (human), 2019-nCoV (human), SARS-CoV (human), Ty-BatCoV_HKU4 (bat) and Ro-BatCoV_HKU9 (bat) [55]

1.5 Coronavirus Replication and Pathogenesis

The life cycle of the coronavirus within the host consists of five steps namely; attachment, penetration, biosynthesis, maturation and release. Once viruses bind to host receptors (attachment), they enter host cells through endocytosis or membrane fusion, and the viral RNA are released inside the host cells, followed by replication and viral mRNA is used to make viral proteins (biosynthesis) with subsequent release of new viral particles [57]. SARS-CoV-2 enters the host cell via the use of angiotensin-converting enzyme 2 (ACE2) as its cellular receptor [58]. ACE2 is a membrane–bound monocarboxypeptidase abundantly present in human cells and is predominantly expressed in different organs including; heart, lungs, kidney, liver, intestine, and pulmonary alveolar (type II) cells [59], [60], [61]. Entry of SARS-CoV-2 into human cells is facilitated by the interaction between the receptor binding domains of the viral spike glycoprotein ectodomain with the ACE2 receptor [55]. On the other hand it was speculated that upregulation of angiotensin converting enzyme 2

(ACE2) could increase the risk of COVID-19, especially in patients with underlying health conditions such as diabetes, hypertension, cardiac diseases [62], because ACE2 is the enzyme that give access for SARS-CoV-2 to enter the cell. ACE2, are found in the lower respiratory tract of humans, is known as cell receptor for SARS-CoV [63], and regulates both the cross-species and human-to-human transmission [64]. From the laboratory investigation of bronchoalveolar lavage fluid (BALF) from a COVID-19 patient, confirmed that the SARS-CoV-2 uses the same cellular entry receptor ACE2 [39], as the other SARS-CoV. The virion S-glycoprotein on the surface of coronavirus can attach to the receptor, ACE2 on the surface of human cells [65]. S glycoprotein includes two subunits, S1 and S2 [66]. S1 determines the virus-host range and cellular tropism with the key function domain − RBD, while S2 mediates virus-cell membrane fusion by two tandem domains, heptad repeats 1 (HR1) [67], and HR2 [68]. After membrane fusion, the viral genome RNA is released into the cytoplasm, and the uncoated RNA commences the translation of the two polyproteins, pp1a and pp1ab [69], which encode non-structural proteins, and form replication-transcription complexes (RTC) in double-membrane vesicle [70]. Immediately, RTC replicate and synthesize a nested set of subgenomic RNAs [71], which encode accessory proteins and structural proteins mediated by endoplasmic reticulum (ER) and Golgi [72], newly formed genomic RNA, nucleocapsid proteins and envelope glycoproteins assemble and form viral particle buds. Lastly, the virion-containing vesicles fuse with the plasma membrane to release the virus. Since the binding of SARS-CoV-2 Spike (S) glycoprotein and ACE2 receptor is a critical step for virus entry. Systematic detection of β-CoV receptors showed that human cells expressing ACE2, but not human Dipeptidyl peptidase-4 (DPP4) or APN (Aminopeptidase N), were enhanced port of entry for SARS-CoV-2 [49], while, it was also detected that S protein and ACE2 binding efficiency was found to be between 10- to 20- fold higher than that of SARS-CoV, evidenced by Cryo -electron microscope (Cryo-EM) Structure of the SARS-CoV-2 Spike in the pre-fusion conformation [73]. However, other studies have shown that up regulation of ACE2 has no clear role in aggravation of the COVID-19 progression, although down regulation of ACE2 can reduce the risk of SARS-CoV-2 infection due to reduced virus receptors [74]. On the other hand smoking has also been perceived as a potential risk factor for COVID-19 patients, which increases expression of ACE2, TMPRSS2, ADAM17 and ACE, which are likely to provide storm access of viral receptors or cofactors for SARS-CoV-2, leading to severe COVID-19 complications. This is linked to the fact that strong associations between air pollution exposure inhaled noxious particles are likely to influence COVID-19 outcomes [75]. Nevertheless evidence to establish that smoking is one of the risk factors in COVID-19 patients is needed [76]. Again it is important to note that underlying cardiovascular diseases are highly associated with increased risk of in-hospital deaths among patients hospitalized with COVID-19 [77]. Recently, another study revealed a novel route of SARS-CoV-2 invasion through spike protein (SP) interaction with transmembrane glycoprotein CD147 [78], in which in *vitro* anti-viral tests showed that meplazumab, an anti-CD147 humanized antibody, inhibited SARS-CoV-2 from invading host cells, this implies that this novel route via CD147 would provide a new target for ani-viral drug development [78].

1.6 Invasion of CNS by SARS-CoV-2

The brain like any other organs expresses the hACE2 which is the entry point of the SARS-CoV-2 virus in humans as such it is not immune to viral infection [79]. From the previous studies with other CoVs, SARS-CoV-2 a member from the same family is likely to infect the peripheral nerve terminals and then penetrate through synapses into the central nerve system (CNS) [80]. In addition reports indicating that infection of gastrointestinal tract by SARS-CoV-2 could even allow the virus to enter via enteric nervous system and its sympathetic afferent neurons then to the CNS [80]. This notion is supported by an experiment in transgenic mice where SARS-CoV and MERS-CoV were administered intranasal and it was observed that the virus infiltrate into the brain through the olfactory nerves, subsequently affecting the thalamus, and the brain stem [79]. Apparently this phenomenon concurs with the current symptoms observed in COVID-19 patients such as involuntary breathing, hyposmia, and ageusia, which is suggestive of the fact that SARS-CoV-2 not only infect lungs but it has severe implications in neurons, particularly the medulla oblongata, that regulate breathing, lungs and heart functions [79].

1.7 Implication of SARS-CoV-2 in brain dysfunction

From CT scan and MRI scan images from the brain of the COVID-19 patients have revealed symptoms of necrotizing hemorrhagic encephalopathy [81], this is likely to cause the brain dysfunction, since most of the brain dysfunction are attributed to viruses. More specifically, SARS-CoV-2 infected patients shows Acute necrotizing encephalopathy (ANE) as revealed by MRI images, possible leading to seizures, liver problems and mental disorientation [79], [81]. It is also of note that COVID-19 seems to affect the brain stem, thalami, cerebellum and cerebral white matter, of which some COVID-19 patients have been reported to have suffered from neurological conditions including; mental health, and inability to taste or smell [26], [79].

1.8 Implication of SARS-CoV-2 in lungs

Current studies are citing the severe impact of SARS-CoV-2/ COVID-19 in human lungs, where histological analyses revealed distinctive vascular features consisting of severe endothelial injury associated with presence of intracellular virus, disrupted cell membranes and widespread thrombosis within pulmonary vascular system. [82], and a COVID-19 patients usually presented with higher fever, and dyspnea with chest radiograph revealed acute invasive lesions in lungs.

1.9 Does SARS-CoV-2 display selective virulence capacity against human?

SARS-CoV-2 the causal agent of COVID-19 is currently raging across the globe with massive infections and un-tolled number of deaths with much more severity in some countries and a bit lesser number of deaths in other countries. This raises several questions why the severity of COVID-19 appears in this manner? To have some clue for this unknown fact, we dwelled on different reports for instance recently it was reported that SARS-CoV-2 has mutated and proliferated into more new strains, among which there are very aggressive strains while other strains seems to be less virulent. The former are the strains believed to have hit some of

the European countries and the Americas, while the latter are those which got transmitted to Africa and parts of Asia. But not with understanding if so none of the mankind should feel safe because the dynamic of this events could change anytime let us imagine that the highly virulent or aggressive strain happen to be transported from Europe to Africa the result would be the same or worse than as seen in those countries which are currently experiencing the worse scenario from COVID-19 pandemic. In addition, recently it was reported that SARS-CoV-2 strain that reached India has variations in its spike surface glycoprotein (Ala930Val), this is in comparison to the strains from USA, Wuhan, Italy, and Nepal [83], and also the study detected the presence of antiviral miRNA, has-miR-27b that is unique to the Indian host population, which binds to mutated region of Indian SARS-CoV-2 strain [83].This was perceived as justification to how anti-HIV regimen was able to cure HIV/AIDS patients in India but the same drug did not work well with HIV/AIDS patients in China [26]. On the other hand use of Calmette-Guerin (BCG) vaccine in countries like India was believed to be responsible in boosting the immunity of communities in such countries, thus serving as protective shields against COVID-19 outbreak [26], contrary to countries which have not exposed their citizens to BCG vaccination are the ones hardly hit with COVID-19 outbreak [26]. Anyway, more investigations are needed to verify such claims.

2. Diagnostic criteria

The viral research institution in China has conducted preliminary identification of the SARS-CoV-2 through the classical Koch's postulates and observing its morphology through electron microscopy, So far, the golden clinical diagnosis method of COVID-19 is nucleic acid detection in the samples from nasal or throat swab, sputum by real-time polymerase chain reaction (rtPCR) and further confirmed by next-generation sequencing [5], [84].

3. Clinical symptoms

A recent reports [85] on COVID-19 laboratory-confirmed cases, found that the severity of the major clinical manifestations include fever, cough, and shortness of breath, but then other atypical symptoms include; Sore throat, fatigue, sputum production, chills, malaise, increased confusion, rhinorrhea or nasal congestion, dizziness, nausea, and headache have also been reported [62], [45], hence COVID- 19 symptoms are invariant. In addition, they found some rare cases among the patients manifested gastrointestinal symptoms, with diarrhea and vomiting. The clinical manifestations were in consistence with the previous results reported in (ESICM, SCCM) [86], in which fever and cough were the dominant symptoms whereas upper respiratory symptoms and gastrointestinal symptoms were rare, this suggest the differences in viral tropism as compared with SARS-CoV [87], MERS CoV, and influenza [88]. However SARS-CoVs patients presented similar symptoms, such as fever, malaise, and cough [89]. Most adults or children with SARS-CoVs infection presented with mild flu-like symptoms but than a few patients may get into critical condition which rapidly developed to acute respiratory distress syndrome, respiratory failure, multiple organ failure, including deaths [90]. But the SARS-CoV-2 infections are more severe and highly contagious than the previous SARS-CoVs.

Moreover, it should be noted that there are challenges associated with the onset of the symptoms of SARS-CoV-2 infections for instance some studies have cited poor correlation between the symptoms onset and the viral shedding among the SARS-CoV-2 infected persons [45], while, other studies suggested that SARS-CoV-2 shedding is highest at earlier in the illness [91], [92], and also reports citing that the SARS-CoV-2 infected patients are capable of shedding the virus for more than 7 days after symptoms onset [45], [93].

4 Therapeutics and Treatment trials

Vaccine is one of the essentially components in the management and prevention of the infectious diseases and it strengthens the output of public health care machinery against the infectious agents. It has been estimated that annually vaccination prevents between 2 to 3 million deaths [94], globally, despite these significant achievements there are many diseases for which vaccine development remains a challenge, for instances most of the diseases caused by viruses, vaccines have not been developed easily because viruses undergo significant antigenic drift or mutation [95], [96]. For example dengue virus (arbovirus) which is estimated to infect ~ 390 million people worldwide each year there is no efficient Dengue vaccine so far and this is attributed to the complexity of the immunopathology [97]. Furthermore, it was reported that SARS-CoV-2 has mutated into many new strains and some of these new strains are presumed to be more virulent than other strains. This in fact adds more complexity and signaled the difficulties which lied ahead in the development of vaccines against SARS-CoV-2. Nonetheless, in the events of any new outbreaks of diseases caused by a new pathogen concerted efforts should be geared towards either discovery of a new drug, or modify the existing therapeutics or develop a vaccine in order to reduce the impact of the pandemic. Indeed COVID-19 has exposed the health systems to serious challenges on global level, infecting more than 11 million people with over 500,000 deaths around the world, yet till now there are no clinically approved antiviral drugs or vaccine available to be used for the treatment of COVID-19 patients. One of the options available is to screen or assess for the effectiveness of the previously approved broad-spectrum antiviral drugs like Nucleoside analogues and HIV-protease inhibitors which are capable of attenuate virus infection or replication as a quick remedy until such a time the anti COVID-19 is found and approved for use [98]. Extensive measures to reduce person-to-person transmission of COVID-19 are required to control the current outbreak. Special attention and efforts to protect or reduce transmission should be applied in susceptible populations including children, health care providers, and elderly people [99]. Currently several drugs are being used under clinical trial and compassionate use protocols based on in vitro activity (against SARS-CoV-2 or related viruses) and on limited clinical experience. Efficacy has not been established for any drug therapy [100]. The FDA continues to investigate the use of NSAIDs in patients with COVID-19 symptoms [101]. Concern for potential worsening of COVID-19 symptoms has been suggested, there is an anecdotal published letter that suggests a link between ibuprofen and increased ACE2 expression that may lead to worse outcomes in COVID19 patients [102]. But acetaminophen may be considered for temperature control [103].

4.1. Chloroquine

Chloroquine is a 9-aminoquinoline that has been known since 1934. Specifically synthesized to be used as an anti-malarial agent, unfortunately chloroquine was dismissed from antimalarial therapy and prophylaxis, due to the continuous emergence of chloroquine-resistant Plasmodium falciparum strains [46]. But due to broad spectrum and antiviral activity of chlrorquine has suppressive effects on the production/release of TNF and interleukin 6 [104]. Chloroquine is known to block virus infection by increasing endosomal pH required for virus/ cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV [105], chloroquine functioned at both entry, and at post-entry stages of the 2019-nCoV infection. Besides its antiviral activity, chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect in vivo. Chloroquine is easily absorbed and distributed in the whole body, including lung, after oral administration [106]. Earlier studies conducted in the French hospital reported about the benefit of hydroxychloroquine for treatment of COVID-19 patients [107], and this was also supported by another randomized trials of 400mg daily of hydroxychloroqiune to the COVID-19 patients, in which they reported that after 7 days of treatment the throat swab tested negative for SARS-CoV-2 load [108]. However, recently another study showed that randomized use of hydroxychloroquine has no distinguishable benefits for the treatment of COVID-19 patients [109], but rather suggested for more randomized trials of hydroxychloroquine prior to its official application in the health care units.

4.2. Remdesivir (GS-5734)

Remdesivir (GS-5734) is an inhibitor of viral RNA dependent, RNA polymerase was earlier recognized as antiviral drug against a wide array of RNA viruses (including SARS/MERS-CoV) infection [104], [110], [111], [112], and its inhibitory effect was also detected against SARS-CoV-2 in vitro [113], [114]. In addition, experiment using remdesiri in nonhuman primate (NHP) models against MERS-CoV revealed reduced virus load in lungs and as well as less damage caused [115], [116]. It is currently under clinical development for the treatment of Ebola virus infection [117]. Remdesivir is an adenosine analogue, which incorporates into nascent viral RNA chains and results in pre-mature termination of the viral replication process [118]. Remdesivir functioned at a stage post virus entry, which is in agreement with its putative antiviral mechanism as a nucleotide analogue. [106]. Recently it was reported that use of remdesiri in the treatment of COVID-19 patients enhanced the recovery process with median time of 11 days in comparison to 15 days placebo care group [119], this result is inconsistent with the previous studies [120], in which the time of clinical improvement for remdesviri treated group was 21 days versus 23 days for the control group. Moreover, serious adverse effects of the remdesviri drug usage was also reported, this again may require further investigations in the use of remdesvir. However, it was speculated that efficacy of remdesviri can be improved by combining with other drugs [119], a claim yet to be verified.

4.3. Lopinavir and Ritonavir:

Lopinavir is a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor with in vitro inhibitory activity against SARS-CoVs [121], [122], [123], also both in vitro [124] and in animal model [125], studies showed potential activity for other corona-viruses MERS-CoV. Ritnovir. is usually combined with lopinavir to increase its plasma half-life via the inhibition of the cytochrome P450, acts by binding to Mpro, a key enzyme for coronavirus replication and this may suppress coronavirus activity [126]. Evidence of Pre-clinical data show activity for other corona-viruses [127], a randomized, controlled, open-label trial involving hospitalized patients with confirmed SARS-CoV-2 infection (n = 199), analyzed treatment with lopinavir; ritonavir. Treatment with lopinavir; ritonavir for 14 days was not associated with a difference from standard care in the time to clinical improvement (hazard ratio 1.24; 95% CI, 0.9 to 1.72). Mortality at 28 days was similar between groups (19.2% vs. 25%, respectively). The percentages of patients with detectable viral RNA were similar. In a modified ITT analysis, lopinavir; ritonavir had a median time to clinical improvement that was shorter by 1 day. A retrospective cohort study of hospitalized patients reviewing clinical course and risk factors for mortality included 29 patients who received lopinavir; ritonavir. It was reported that the number of patients treated with Lopinavir-ritnovir against COVID-19, who had serious complications or requiring noninvasive or invasive mechanical ventilators for respiratory failure were fewer than in those not receiving treatment [129], however, it is not clear whether intervention by lopinavir-ritonavir against COVID-19 at certain stage of disease progression may reduce some complication [126], also in comparison the gastrointestinal adverse events such as anorexia, nausea, abdominal discomfort, or diarrhea tended to be more in the patients under lopinavir-ritonavir treatment than the patients under standard-care but again more serious advents events were prominent among the patients under standard-care [126]. On the other hand it was reported that treatment of the COVID-19 patients using lopinavir-ritonavir regimens does not enhance effective clinical improvement, nor reduce the mortality rate in a serious COVID-19 patients [126], but acknowledged that the lopinavir-ritonavir patients spend shorter time in intensive care unit (ICU) than those in the standard-care with minimum of 6 days versus 11 days respectively [126]. On the protein-drug interactions it was reported that lopinavir complex involves three H-bonds within the active site of SARS-CoV-2, [128], while ritonavir complex consists of four H-bonds also within the SARS-CoV-2 active sites, in both cases two residues (E166 and Q189) appeared to be critical in these process. This concurs with the protein-drug bindings with HIV-1 protease inhibitor with SARS-CoV [129]. Furthermore, recently [130], reported on the first randomized triple drug trial, and the triple combination includes; interferon beta-1b, lopinavir-ritonavir and ribavirin drugs administered to COVID-19 patients. They found that the triple combination of these drugs is more effective than when each is administered singly in the treatment of the COVID-19 patients. The combined regimen had shorter treatment duration with the median time of 7 days in comparison to control group which has the median range of 12 days [130], but they noted that other adverse conditions for instances nausea, diarrhea, persisted in both groups.

4.4. Tocilizumab

Tocilizumab is an Interleukin-6 (IL-6) Receptor-Inhibiting Monoclonal Antibody Rationale for Use: Cytokine release syndrome may be a component of severe disease in COVID-19 patients. Evidence / Experience: A retrospective review analyzed 21 patients in which tocilizumab were added to standard COVID-19 therapy. Preliminary data suggest tocilizumab may have clinical benefit as adjunctive therapy. Clinical symptoms, CT opacity changes, lymphocyte percentage, and Creative protein levels all improved in these patients; however, no comparators were reported, although some suggestions were recommended for use [84]. Tocilizumab acts by inhibiting IL-6-mediated signaling by competitively binding to both soluble and membrane-bound IL-6 receptors. IL-6 is a pro-inflammatory cytokine that is involved in diverse physiological processes such as T-cell activation, immunoglobulin secretion induction, hepatic acute-phase protein synthesis initiation, and hematopoietic precursor cell proliferation and differentiation stimulation. Caution in patients with thrombocytopenia and neutropenia, Infusion-related reactions [131].

4.5. COVID-19 Convalescent Plasma

Plasma collected from persons who have recovered from COVID-19 that may contain antibodies to SARS-CoV-2 Rationale for Use: Clinical trials are being conducted to evaluate the use of COVID-19 convalescent plasma to treat patients with severe or immediately life-threatening COVID-19 infections. COVID-19 convalescent plasma is not intended for prevention of the infection [132]. Other drugs such as; Azithromycin: Macrolide Antibacterial, Azithromycin may prevent bacterial superinfection, and macrolides may have immunomodulatory properties to assist as adjunct / supportive therapy. Macrolides may have immune-modulatory properties in pulmonary inflammatory disorders. They may down regulate inflammatory responses and reduce the excessive cytokine production associated with respiratory viral infections; however, their direct effects on viral clearance are uncertain. Immunomodulatory mechanisms may include reducing chemotaxis of neutrophils (PMNs) to the lungs by inhibiting cytokines (i.e., IL-8), inhibition of mucus hyper-secretion, and decreased production of reactive oxygen species, accelerating neutrophil apoptosis, and blocking the activation of nuclear transcription factors. Evidence / Experience: o in an open-label, non-randomized clinical trial of hydroxychloroquine (n = 26), azithromycin was administered in combination with hydroxychloroquine to prevent bacterial super-infection. Preliminary data suggest the potential for benefit as adjunct therapy. On day 6, all patients treated with the combination (hydroxychloroquine and azithromycin) were virologically cured compared to 57.1% of patients treated with hydroxychloroquine alone (n= 20). Safety Concerns: Risk of cardiac arrhythmias (e.g., QT prolongation) of significant drug interactions. Other immunomodulating agents (e.g., alfa-interferon, sarilumab) are being evaluated as adjunctive therapy [133].

5. Discussion

SARS-CoV-2 is the causative agent of COVID-19 pandemic, a newly emerged disease that is highly contagious causing a typical pneumonia with varied fatality rates estimated between 0.2% to 2.4%, [5]. Of course as a new disease outbreak there is no immediate cure or vaccine available to curb the spread of SARS-

CoV-2 infections. Hence, the current efforts are based on randomized clinical trials of various classes of antiviral drugs especially those with broad spectrum of antivirus, for instance remdesivir an adenosine analogue against wide range of RNA viruses has been used for the treatment of Ebola virus [117], with 100% protection activity. The drug acts at the post viral entry which is crucial in arresting the subsequent progressive stages of the virus. Nucleoside analogues and HIV-protease inhibitors are effective against viral infectivity and replication [98]. Chloroquine, an anti-malaria drug that has been band for some years due to encountered resistant by plasmodium flaciparum strain [46], has surfaced again as a trial drug of choice against COVID-19, because of its broad-spectrum as antiviral medicine. Chloroquine is presumed to block the virus infection by increasing the endosomal pH necessary for viral/cell fusion interface and also interfering with the glycosylation of cellular receptors of SARS-CoV [105]. Studies in animal model and in vitro assays have shown that other HIV- protease inhibitors such as Lopinavir and Ritonavir are potential drugs effective in arresting the progression of SARS-CoV and MERS-CoV [126], therefore, it is likely that these drugs may function in similar way in SARS-CoV- 2. Perhaps understanding modes of action and specificity/ sensitivity of these drugs are essentially important in winning the fight against the COVID-19 pandemic. Although, studies by [126], reported that lopinavir and ritonavir treatment of COVID-19 patients did not make any substantially clinical improvement, presumably the timing for intervention at the onset of infection may play a crucial role but this warrants an investigation. However, more reports are indicating that these drugs (liponavir and ritonavir) are becoming of more importance in the treatment of COVID-19 patients because recently it was reported that both liponavir and ritonavir formed complexes with SARS-CoV-2 at its active site, and also two residues E166 and Q189 were identified to be critical in the formation of the complexes [128]. This suggested that these drugs are most likely to help in the treatment of COVID-19. Recently, it was reported that triple combination of interferon beta-1b, lopinavir-ritonavir and ribavirin drugs used in the treatment of COVID-19 patients has shown better improvement in the symptoms and with reduced treatment time of ~ 7days in comparison to the standard treatment care of ~ 12 days [130].

Tocilizumab is an interleukin 6 (IL-6) receptor inhibiting monoclonal antibody which is believed to have clinical benefits as adjunctive therapy and was reported to confer/attain significant improvement in clinical symptoms including; CT opacity, amount of lymphocyte and level of creative proteins [84]. Convalescent plasma obtained from recovered COVID-19 patients containing antibodies are being used for the treatment of very serious life threatening COVID-19 cases [132]. In addition, other adjunctive antibacterial drugs such as Azithromycin are also employed in the treatment of COVID-19 cases as preventive medicine against super-infection by bacteria. Moreover, combine treatment using hydroxychloroquine and azithromycin was reported to be very effective against the COVID-19 patients in comparison to when hydroxychloroquine was used alone. On the other hand recent reports are suggesting the use of triple drug combination of interferon-beta 1b, lopinavir-ritonavir and ribavirin to be more effective against SARS-CoV-2 than when each is used singly [130]. Unfortunately, several studies are suggesting different drugs for the treatment of COVID-19

patients, some are suggesting the use of hydroxychloroquine or in combination with azithromycin, while other are citing the use of triple combination of interferon beta 1b, lopinavir-ritonavir and ribavirin [130]. Despite all of these numerous suggestions of drugs which are currently on clinical trial against COVID_19 patients, yet none has been found to be effective, hence, more studies are warranted to discover the real anti-COVID-19 drug or vaccine but it is quite arguable that there is need to ascertain the efficacy of these drugs against SARS-CoV-2 prior to its usage.

Nonetheless, from the experiences it is obvious that most of the viral diseases posed very serious challenge to health care systems as such the option for vaccines may not be the best one for many reasons; peoples' perception or lack of confidence in vaccine safety and perhaps its adverse effects [134]. In addition, viruses undergo significant antigenic drift or mutation [95], [96]. For instance till now there is no effective vaccine against Dengue fever, this is partially blamed on the complexity of the immunopathology [97], also the SARS-CoV the causative agent of sever acute respiratory syndrome (SARS) which occurred in some countries including China, in 2002-2003, even there is no effective vaccine developed to date against SARS-CoV. Apparently, it has been reported that SARS-CoV-2 that emerged few months ago has already mutated many times producing number of new strains, in which some of these new SARS-CoV-2 strains are presumed to be potential virulent than other strains. In addition, SARS-CoV-2 strain carrying mutated spike D914G [135], appears to be predominant in most regions replacing the original SARS-CoV-2 strain from Wuhan. This raises a concern whether this particular mutant strain confers certain ability to the virus, and this in fact adds more complexity and underlined the difficulties ahead in the development of effective vaccine against SARS-CoV-2. At the moment it is not known whether these mutations are making the SARS-CoV-2 to become more or less lethal?

However, it should be understood that the prevention and control measures against COVID-19 outbreak is very challenging due to the inadequacy of diagnostics, isolation and quarantine facilities in most of the public health care systems across the world especially in the third world countries. Another scenario is the danger posed by asymptomatic and pre-symptomatic individual carriers of SARS-CoV-2, which may be potential source of transmission to other healthy people within the population [45], [136]. Furthermore, the time between SARS-CoV-2 infection and the onset of the illness which takes between 2-14 days, this presents additional problem prior to the identification and isolation of positive cases at an earlier stage of disease [137]. It is important to understand that screening for COVID-19 cases should not be based solely on symptomatic strategy since, asymptomatic and presymptomatic stages of SARS-CoV-2 are equally found to have high virus titer similar to symptomatic infection [45], [138], [139], [140], hence, shedding viable virus during this period are potential suit for transmission. Therefore, as the pandemic evolves enforcement of more effective preventive and control measures or guidelines ushered by public health authorities, world health organization and "CDC" against spread of COVID-19 pandemic, such as mandatory wearing of face masks in public places, observing social distancing, mandatory clinical testing of citizens for COVID-19 cases and prohibiting

sharing of medical devices are important at this point in time, in order to reduce rapid transmission of SARS-CoV-2 in the communities. Moreover, the case definition also need to be redefined as COVID-19 appears to infect several organs within the human body such as lungs, liver, brain, testis, neurological system, gastrointestinal complications leading to number of diseases which include; pneumonia, hypoxia, aguesa, diarrhea, etc. [79], [81], [82], [141], thus signifying the gravity of COVID-19 pandemic. Despite the mixed versions of reports saying that immunity protection seems to be present only in the small percentage among the recovered COVID-19 patients, indicating that the antibodies produced against SARS-COV-2 infection/ COVID-19 have short life. Hence, it is not clear whether herd immunity from the COVID-19 survivors may be beneficial enough to fill the gap prior to the development of any anti-SARS-CoV-2/ COVID-19 drug or vaccine, it remains elusive.

6. Conclusion

In this review we obtained the relevant information from articles and focused much on therapeutics currently being used against COVID-19, however, as the knowledge on SARS-CoV-2/COVID-19 pandemic is still evolving, we summarized the current trends of events related to the origin, transmission, pathogenesis, challenges and possibilities associated with the efficacy of treatment against COVID-19 patients using different antiviral drugs. Unfortunately, no any anti-SARS-CoV-2/ COVID-19 drug have been developed yet so far. Thus, it should be noted that understanding the molecular basis of SARS-CoV-2, crystal structures are essential for designing drugs which could have specific target within the virus particle. In the light of the continued threat pose by SARS-CoV-2 infections, it is clear that COVID-19 has come to stay for a while with the mankind, although, there are number of already existing drugs on clinical trials in different countries and as efforts are being exerted across the world in numerous laboratories in the search for a new drug or vaccine against the SARS-CoV-2 to curb the spread of COVID-19 pandemic, it is quite tempting to speculate that this scenario may drag longer than presumed at the start of this pandemic. The lessons learned might help in earlier preparations for the future outbreaks of epidemics/ pandemics of similar magnitude.

7. Future Perspectives

After declaration of COVID-19 as global pandemic by World Health Organization (WHO), and up to this moment its causal agent SARS-CoV-2 is still evolving and rapidly infecting more people in systematic manner. This definitely necessitates for concerted and more collaborative researche investigations at global scale so as to gather scientific evidences on the biology of SARS-CoV-2. Since many reports are citing that SARS-CoV-2 has continued to spontaneously mutate resulting in production of new strains, of which some of these strains are suspected to be more virulent and mortal than other strains but it is not known at the moment whether the mutant strains are more or less lethal. Therefore, understanding the molecular strategy of SARS-CoV-2 in pathogenesis is very important in designing or development of anti SARS-CoV-2 drugs and vaccines.

8. Declarations

8.1 Study Limitations

COVID-19 pandemic is a newly emerged disease consequently the detailed understanding and accurate knowledge about the SARS-CoV-2 biology is still evolving, hence many published papers/articles might contain some information which are likely to be redefined. Since our review manuscript is based on the published articles our work is subject to challenge in the event of any new findings.

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8.5. Competing Interests

The authors declare no competing interests

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