COVID-19

INTRODUCTION

Over the past 2 decades, coronaviruses (CoVs) have been associated with significant disease outbreaks in East Asia and the Middle East. The severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) began to emerge in 2002 and 2012, respectively. Recently, a novel coronavirus, sever acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), emerged in late 2019, and it has posed a global health threat, causing an ongoing pandemic in many countries and territories (1).

Health workers worldwide are currently making efforts to control further disease outbreaks caused by the novel CoV (originally named 2019-nCoV), which was first identified in Wuhan City, Hubei Province, China, on 12 December 2019. On 11 February 2020, the World Health Organization (WHO) announced the official designation for the current CoV- associated disease to be COVID-19, caused by SARS-CoV-2. The primary cluster of patients was found to be connected with the Huanan South China Seafood Market in Wuhan (2).

CoVs belong to the family Coronaviridae (subfamily Coronavirinae), the members of which infect a broad

trimeric SI locates itself on top of the trimeric S2 stalk (45). Recently, structural analysis of the S proteins of COVID-19 have revealed 27 amino acid substitutiona within a 1,273-amino-acid stretch (16). Six substitutions are located in the RBD (amino acids 375 to 528), while four substitutions are in the RBM at the CTD of the SI domain (16). Of note, no amino acid change is seen in the RBM, which binds directly to the angiotensin-converting enzyme-2 (ACE2) receptor in SARS- CoV (16, 46). At present, the main emphasis in knowing how many differences would be required to change the host tropism. Sequence comparison revealed 17 non-synonymous changes between the early sequence of SARS-CoV-2 and the later isolates of SARS-CoV. The changes were found scattered over the genome of the virus, with nine substitutions in ORF1ab, ORF8 (4 substitutions), the spike gene (3 substitutions), and ORF7a (single substitutions) (4). Notably, the same nonsynonymous changes were found in a familial cluster, indicating that the viral evolution happened during person-to-person transmission (4, 47). Such adaptive evolution events are frequent and constitute a constantly ongoing process once the virus spreads among new hosts (47). Even though no functional changes occur in the virus associated with this adaptive evolution, close monitoring of the viral

absence of this protein is related to the altered virulence of coronaviruses due to changes in morphology and tropism (54). The E protein consists of three domains, namely, a short hydrophilic amino terminal, a large hydrophobic transmembrane domain, and an efficient C-terminal domain (51). The SARS -CoV-2 E protein reveals a similar amino acid constitution without any substitution (16).

N Protein

The N protein of coronavirus is multipurpose. Among several functions, it plays a role in complex formation with the viral genome, facilities M protein interaction needed during virion assembly, and enhances the transcription efficiency of the virus (55, 56) . It contains three highly conserved and distinct domains, namely, an NTD, an RNA-binding domain or a linker region (LKR), and a CTD (57). The NTD binds with the 3' end of the viral genome, perhaps via electrostatic interactions, and is highly diverged both in length and sequence (58). The charged LKR is serine and arginine rich and is also known as the SR (serine and arginine) domain (59). The LKR is capable of direct interaction with in vitro RNA interaction and is responsible for cell signaling (60, 61). It also modulates the antiviral response of the host by working as an antagonist for interferon

nsps and Accessory Proteins

Besides the important structural proteins, the SARS-CoV-2 genome contains 15 nsps, nsp1 to nsp10 and nsp12 to nsp16, and 8 accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, and ORF14) (16). All these proteins play a specific role in viral replication (27). Unlike the accessory proteins of SARS-CoV, SARS-CoV-2 does not contain 8a protein and has a longer 8b and shorter 3b protein (16). The nsp7, nsp13, envelope, matrix, and p6 and 8b accessory proteins have not been detected with any amino acid substitutions compared to the sequences of other coronaviruses (16).

The virus structure of SARS-CoV-2 is depicted in

Fig. 2.

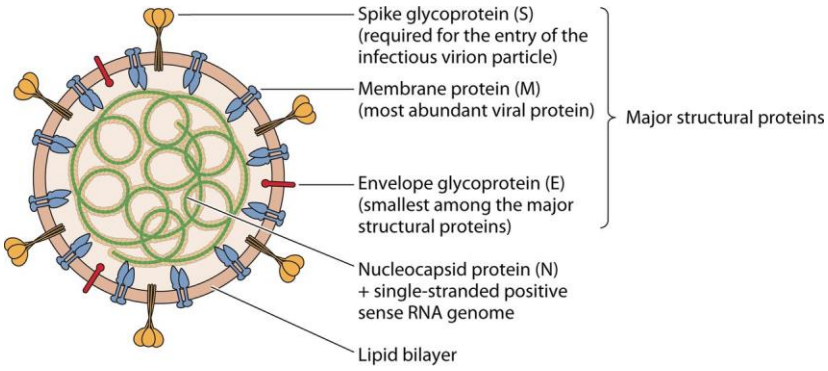

FIG 2 SARS-CoV-2 virus structure.

Initially, the epicenter of the SARS-CoV-2 pandemic was China, which reported a significant number of deaths associated with COVID-19, with 84,458 laboratory-confirmed cases and 4644 deaths as of 13 May 2020 (Fig. 4). As of 13 May 2020, SARS-CoV-2 confirmed cases have been reported in more than 210 countries apart from China (Fig. 3 and 4) (WHO Situation Report 114) (25, 64). COVID-19 has been reported on all continents except Antarctica. For many weeks, Italy was the focus of concerns regarding the large number of cases, with 221,216 cases and 30,911 deaths, but now, the United States is the country with the largest number of cases, 1,322,054, and 79,634 deaths. Now, the United Kingdom has even more cases (226, 4671) and deaths (32, 692) than Italy. A John Hopkins University web platform has provided daily updates on the basic epidemiology of the COVID-19 outbreak

COVID-19 has also been confirmed on a cruise ship, named Diamond Princess, quarantined in Japanese waters (Port of Yokohama), as well as on other cruise ships around the world (239) (Fig.3). The significant events of the SARS-CoV-2/COVID-19 virus outbreak occurring since 8 December 2019 are presented as a timeline in Fig. 5.

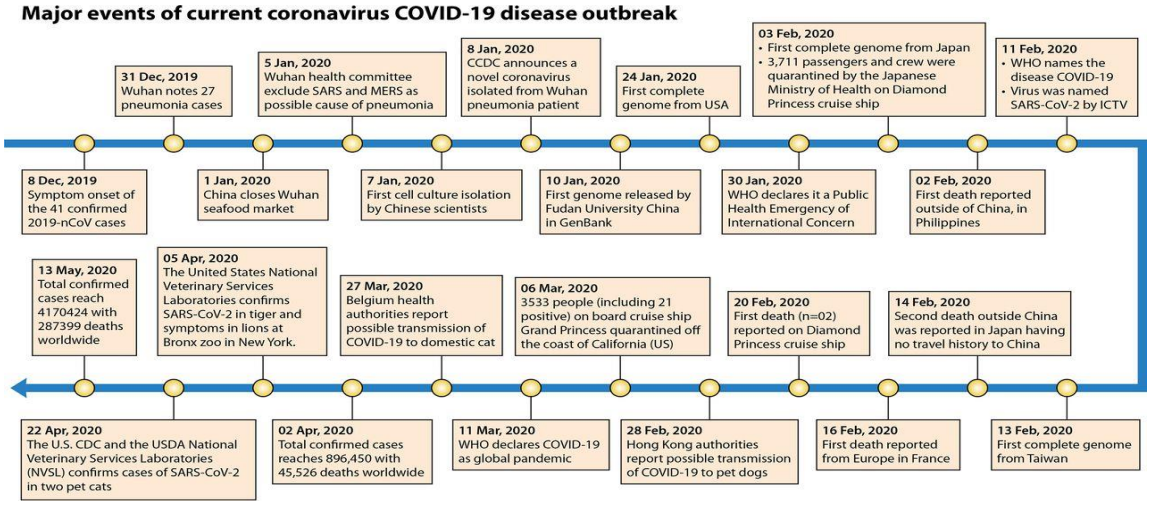

FIG 5

Timeline depicting the significant events that occurred during the SARS-CoV-2/COVID-19 virus outbreak. The timeline describes the significant events during the current SARS-CoV-2 outbreak, from 8 December 2019 to 13 May 2020.

At the beginning, China experienced the majority of the burden associated with COVID-19 in the form of disease morbidity and mortality (65), but over time the COVID-19 menace moved to Europe, particularly Italy and Spain, and now the United States has the highest number of confirmed cases

another study, the average reproductive number of COVID-19 was found to be 3.28, which is significantly higher than the initial WHO estimate of 1.4 to 2.5 (77). It is too early to obtain the exact R0 value, since there is a possibility of bias due to insufficient data. The higher R0 value is indicative of the more significant potential of SARS-CoV-19 transmission in a susceptible population. This is not the first time where the culinary practices of China have been blamed for the origin of novel coronavirus infection in humans. Previously, the animals present in the live-animal market were identified to be the intermediate hosts of the SARS outbreak in China (78). Several wildlife species were found to harbor potentially evolving coronavirus strains that can overcome the species barrier (79). One of the main principles of Chinese food culture is that live-slaughtered animals are considered more nutritious (5).

After 4 months of struggle that lasted from December 2019 to March 2020, the COVID-19 situation now seems under control in China. The wet animal markets have reopened, and people have started buying bats, dogs, cats, birds, scorpions, badgers, rabbits, pangolins (scaly anteaters), minks, soup from palm civet, ostriches, hamsters, snapping turtles, ducks, fish Siamese crocodiles, and other

as an entry receptor while exhibiting an RBD similar to that of SARS-CoV (17, 87, 254, 255). Several countries have provided recommendations to their people travelling to China (88, 89). Compared to the previous coronavirus outbreaks caused by SARS-CoV and MERS-CoV, the efficiency of SARS-CoV-2 human-to-human transmission was thought to be less. This assumption was based on the finding that health workers were affected less than they were in previous outbreaks of fatal coronaviruses (2). Superspreading events are considered the main culprit for the extensive transmission of SARS and MERS (90, 91). Almost half of the MERS-CoV cases reported in Saudi Arabia are of secondary origin that occurred through contact with infected asymptomatic or symptomatic individuals through human-to-human transmission (92). The occurrence of superspreading events in the COVID-19 outbreak cannot be ruled out until it's possibility is evaluated. Like SARS and MERS, COVID-19 can also infect the lower respiratory tract, with milder symptoms (27). The basic reproduction number of COVID-19 has been found to be in the range of 2.8 to 3.3 based on real-time reports and 3.2 to 3.9 based on predicted infected cases (84).

route warrants the introduction of negative fecal viral nucleic acid test results as one of the additional discharge criteria in laboratory-confirmed cases of COVID-19 (326).

The COVID-19 pandemic does not have any novel factors, other than the genetically unique pathogen and a further possible reservoir. The cause and the likely future outcome are just repetitions of our previous interactions with fatal coronaviruses. The only difference is the time of occurrence and the genetic distinctness of the pathogen involved. Mutations on the RBD of CoVs facilitated their capability of infecting newer hosts, thereby expanding their reach to all corners of the world (85). This is a potential threat to the health of both animals and humans. Advanced studies using Bayesian phylogeographic reconstruction identified the most probable origin of SARS-CoV-2 as the bat SARS-like coronavirus, circulating in the Rhinolophus bat family (86).

Phylogenetic analysis of 10 whole-genome sequences of SARS-CoV-2 showed that they are related to two CoVs of bat origin, namely, bat-SL-CoVZC45 and bat-SL-CoVZXC21, which were reported during 2018 in China (17). It was reported that SARS-CoV-2 had been confirmed to use ACE2 as an entry receptor while exhibiting an RBD similar

fever, cough, and sputum (83). Hence, the clinicians must be on the look-out for the possible occurrence of atypical clinical manifestations to avoid the possibility of missed diagnosis. The early transmission ability of SARS-CoV-2 was found to be similar to or slightly higher than that of SARS-CoV, reflecting that it could be controlled despite moderate to high transmissibility (84).

Increasing reports of SARS-CoV-2 in sewage and wastewater warrants the need for further investigation due to the possibility of fecal-oral transmission. SARS-CoV-2 present in environmental compartments such as soil and water will finally end up in the wastewater and sewage sludge of treatment plants (328). Therefore, we have to reevaluate that current wastewater and sewage sludge treatment procedures and introduce advanced techniques that are specific and effective against SARS-CoV-2. Since there is active shedding of SARS-CoV-2 in the stool, the prevalence of infections in a large population can be studied using wastewater-based epidemiology. Recently, reverse transcription-quantitative PCR (RT-qPCR) was used to enumerate the copies of SARS-CoV-2 RNA concentrated from wastewater collected from a wastewater treatment plant (327). The calculated viral RNA copy numbers determine the number of infected individuals.

The whole world is suffering from novel SARS-CoV-2, with more than 4,170,424 cases and 287,399 deaths across the globe. There is an urgent need for a rational international campaign against the unhealthy food practices of China to encourage the sellers to increase hygienic food practices or close the crude live-dead animal wet markets. There is a need to modify food policies at national and international levels to avoid further life threats and economic consequences from any emerging or reemerging pandemic due to close animal-human interaction (285).

Even though individuals of all ages and sexes are susceptible to COVID-19, older people with an underlying chronic disease are more likely to become severely infected (80). Recently, individuals with asymptomatic infection were also found to act as a source of infection to susceptible individuals (81). Both the asymptomatic and symptomatic patients secrete similar viral loads, which indicates that the transmission capacity of asymptomatic or minimally symptomatic patients is very high. Thus, SARS-CoV-2 transmission can happen early in the course of infection (82). Atypical clinical manifestations have also been reported in COVID-19 in which the only reporting symptom was fatigue. Such patients may lack respiratory signs, such as cough, fever, and sputum (83).

Hence, the clinicians turtles, ducks, fish, Siamese crocodiles, and other animals meats without any fear of COVID-19. The Chinese government is encouraging people to feel they can return to Normalcy. However, this could be a risk, as it has been mentioned in advisories that people should avoid contact with live-dead animals as much as possible, as SARS-CoV-2 has shown zoonotic spillover. Additionally, we cannot rule out the possibility of new mutations in the same virus being closely related to contact with both animals and humans at the market (284). In January 2020, China imposed a temporary ban on the sale of live-dead animals in wet markets. However, now hundreds of such wet markets have been reopened without optimizing standard food safety and sanitation practices (286).

With China being the most populated country in the world and due to it's domestic and international food exportation policies, the whole world is now facing the menace of COVID-19, including China itself. Wet markets of live-dead animals do not maintain strict food hygienic practice. Fresh blood splashes are present everywhere, on the floor and tabletops, and such food customs could encourage many pathogens to adapt, mutate, and jump the species barrier. As a result, the whole world is suffering from Novel SARS-CoV-2SARS-CoV-2.

With more than, From experience with several outbreaks associated with known emerging viruses, higher pathogenicity of a virus is often associated with lower transmissibility. Compared to emerging viruses like Ebola virus, avian H7N9, SARS-CoV, and MERS-CoV, SARS-CoV-2 has relatively lower pathogenicity and moderate transmissibility (15). The risk of death among individuals infected with COVID-19 was calculated using the infection fatality risk (IFR). The IFR was found to be in the range of 0.3% to 0.6%, which is comparable to that of a previous Asian influenza pandemic (1957 to 1958) (73, 277).

Notably, the reanalysis of the COVID-19 pandemic curve from the initial cluster of cases pointed to considerable human-to-human transmission. It is opined that the exposure history of SARS-CoV-2 at the Wuhan seafood market originated from human-to-human transmission rather than animal-to-human transmission (74); however in light of the zoonotic spillover in COVID-19, is too early to fully endorse this idea (1). Following the initial infection, human-to-human transmission has been observed with a preliminary reproduction number (R0) estimate of 1.4 to 2.5 (70, 75), and recently it is estimated to be 2.24 to 3.58 (76).

In another study, the average reproductive number of possible origin of SARS-CoV-2 and the first mode of disease transmission are not yet identified (70). Analysis of the initial cluster of infections suggests that the infected individuals had a common exposure point, a seafood market in Wuhan, Hubei Province, China (Fig.6). The restaurants of this market are well-known for providing different types of wild animals for human consumption (71). The Huanan South China Seafood market also sells live animals, such as poultry, bats, snakes and marmots (72). This might be the point where zoonotic (animal-to-human) transmission occurred (71). Although SARS-CoV-2 is alleged to have originated from an animal host (zoonotic origin) with further human-to-human transmission (Fig. 6), the likelihood of foodborne transmission should be ruled out with further investigations, since it is a latent possibility (1). Additionally, other potential and expected routes would be associated with transmission, as in other respiratory viruses, by direct contact, such as shaking contaminated hands, or by direct contact with contaminated surfaces (fig. 6). Still, whether blood transfusion and organ transplantation (276), as well as trans-placental and perinatal routes, are possible routes for SARS-CoV-2 transmission needs to be determined (Fig.6).

The newly emerged SARS-CoV-2 is a group 2B coronavirus (2). The genome sequences of SARS-CoV-2 obtained from patients share 79.5% sequence similarities to the sequence of SARS-CoV (63).

As of 13 May 2020, a total of 4,170,424 confirmed cases of COVID-19 (with 287,399 deaths) have been reported in more than 210 affected countries worldwide (WHO Situation Report 114)

and deaths. The COVID-19 outbreaks has also been associated with severe economic impacts globally due to the sudden interruption of global trade and supply chains that forced multinational companies to make decisions that led to significant economic losses (66). The recent increase in the number of confirmed critically ill patients with COVID-19 has already surpassed the intensive care supplies , limiting intensive care services to only a small portion of critically ill patients (67). This might also have contributed to the increased case fatality rate observed in the COVID-19 outbreak.

Viewpoint on SARS-CoV-2 Transmission, Spread, and Emergence

The novel coronavirus was identified within 1 month (28 days) of the outbreak. This is impressively fast compared to the time taken to identify SARS-CoV reported in Foshan, Guangdong Province, China (125 days) (68). Immediately after the confirmation of viral etiology, the Chinese virologists rapidly released the genomic sequence of SARS-CoV-2, which played a crucial role in controlling the spread of this newly emerged novel coronavirus to other parts of the world (69). The possible origin of SARS-CoV-2 and the first mode of

We assessed the nucleotide percent similarity using the MegAlign software program, where the similarity between the novel SARS-CoV-2 isolates was in the range of **99.4% to 100%.** Among the other Serbecovirus CoV sequences, the novel SARS-CoV-2 sequences revealed the highest similarity to bat-SL-CoV, with nucleotide percent identity ranges between **88.12 and 89.65%.** Meanwhile, earlier reported SARS-CoVs showed **70.6 to 74.9%** similarity to SARS-CoV-2 at the nucleotide level. Further, the nucleotide percent similarity was **55.4%, 45.5%** to **47.9%, 46.2% to 46.6%,** and **45.0% to 46.3%** to the other four subgenera, namely, **Hibecovirus, Nobecovirus, Merbecovirus, and Embecovirus**, respectively. The percent similarity index of current outbreak isolates indicates a close relationship between SARS-CoV-2 isolates and bat-SL-CoV, indicating a common origin. However, particular pieces of evidence based on further complete genomic analysis of current isolates are necessary to draw any conclusions, although it was ascertained that the current novel SARS-CoV-2 isolates belong to the subgenus Sarbecovirus in the diverse range of beta-coronaviruses. Their possible ancestor was hypothesized to be from bat CoV strains, wherein bats might have played a crucial role in harboring this class of viruses.

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N Protein

The N protein of coronavirus is multi-purpose. Among several functions, it plays a role in complex formation with the viral genome, facilitates M protein interaction needed during virion assembly, and enhances the transcription efficiency of the virus (55, 56). It contains three highly conserved and distinct domains, namely, an NTD, an RNA-binding domain or a linker region (LKR), and a CTD (57). The NTD binds with the 3' end of the viral genome, perhaps via electrostatic interactions, and is highly diverged both in length and sequence (58). The charged LKR is serine and arginine rich and is also known as the SR (serine and arginine) domain (59).

The LKR is capable of direct interaction with in vitro RNA interaction and is responsible for cell signaling (60, 61). It also modulates the antiviral response of the host by working as an antagonist for interferon (IFN) and (RNA) interference (62). Compared to that of SARS-CoV, the N protein of SARS-CoV-2 possess five amino acid mutations, where two are in the intrinsically dispersed region (IDR; positions 25 and 26), one each in the NTD (position 103), LKR (position 217), and CTD (position 334) (16).

nsps and Accessory Proteins

adaptive evolution, close monitoring of the viral mutations that occur during subsequent human-to-human transmission is warranted.

M Protein

The M protein is the most abundant viral protein present in the virion particle, giving a definite shape to the viral envelope (48). It binds to the nucleocapsid and acts as a central organizer of coronavirus assembly (49). Coronavirus M proteins are highly diverse in amino acid contents but maintain overall structural similarity within different genera (50). The M protein has three trans- membrane domains, flanked by a short amino terminus outside the virion and a long carboxy terminus inside the virion (50). Overall, the viral scaffold is maintained by M-M interaction. Of note, the M protein of SARS-CoV-2 does not have an amino acid substitution compared to that of SARS- CoV (16).

E Protein

The coronavirus E protein is the most enigmatic and smallest of the major structural proteins (51). It plays a multifunctional role in the pathogenesis, assembly, and release of the virus (52). It is a small integral membrane polypeptide that acts as a viroporin (ion channel) (53).

The in-activation or coronavirus S protein is a large, multifunctional class 1 viral trans-membrane protein. The size of this abundant S protein varies from 1,160 amino acids (IBV, infectious bronchitis virus, in poultry) to 1,400 amino acids (FCoV, feline coronavirus) (43). It lies in a trimer on the virion surface, giving the virion a corona or crown-like appearance. Functionally it is required for the entry of the infectious virion particles into the cell through interaction with various host cellular receptors (44).

Furthermore, it acts as a critical factor for tissues tropism and the determination of host range (45). Notably, S protein is one of the vital immuno-dominant proteins of CoVs capable of inducing host immune responses (45). The ectodomains in all CoVs S protein have similar domain organizations, divided into two subunits, S1 and S2 (43). The first one, S1, helps in host receptor binding, while the second one, S2, accounts for fusion. The former (S1) is further divided into two subdomains, namely, the N-terminal domain (NTD) and C- terminal domain (CTD). Both of these subdomains act as receptor-binding domains, interacting efficiently with various host receptors (45). The S1 CTD contains the receptor-binding motif (RBM). In each coronavirus spike protein, the turmeric S1 locates itself on the top of the turmeric S2.

Cat and camels, respectively, act as amplifier hosts (40, 41).

Coronavirus genomes and sub-genomes encode six ORFs (31). The majority of the 5' end is occupied by ORF1a/b, which produces 16 nsps. The two poly-proteins, pp 1a and pp 1ab, are initially produced from ORF1a/b by a -1 frame-shift between ORF1a and ORF1b (32). The virus-encoded proteases cleave poly-proteins into individuals nsps (main protease [Mpro], chymotrypsin-like protease [3CLpro], and papain-like proteases [PLPs]) (42). SARS-CoV-2 also encodes these nsps, and their functions have been elucidated recently (31). Remarkable, a difference between SARS-CoV-2 and other CoVs is the identification of a novel short putative protein within the ORF3 band, a secreted protein with an alpha helix and beta-sheet with six strands encoded by ORF8 (31).

Coronaviruses encode four major structural proteins, namely, spike (S), membrane (M), envelope (E), and nucleocapsid (N), which are described in detail below.

S Glyco-protein

Coronavirus S protein is a large, multifunctional class 1 viral trans-membrane protein. The size of this based on molecular characterization, SARS-CoV-2 is considered a new Beta-coronavirus belonging to the subgenus Sarbecovirus (3). A few other critical zoonotic viruses (MERS-related CoV and SARS-related CoV) belongs to the same genus. However, SARS-CoV-2 was identified as a distinct virus based on the percent identity with other Beta-coronavirus; conserved open reading frame 1a/b (ORF1a/b) is below **90%** identity (3). An overall **80%** nucleotide identity was observed between SARS-CoV-2 and the original SARS-CoV, along with **89%** identity with ZC45 and ZXC21 SARS-related CoVs of bats (2, 31, 36). In addition, **82%** identity has been observed between SARS-CoV-2 and human SARS-CoV Tor2 and human SARS-COV BJ01 2003 (31). A sequence identity of only **51.8%** was observed between MERS-related CoV and the recently emerged SARS-COV-2 (37). Phylogenetic analysis of the structural genes also revealed that SARS-CoV-2 is closer to bat SARS-related CoV. Therefore, SARS-CoV-2 might have originated from bats, while other amplifier hosts might have played a role in disease transmission to humans (31). Of note, the other two zoonotic CoVs (MERS-related CoV and SARS-related CoV) also originated from bats (38, 39). Nevertheless, for SARS and MERS, civet

encircled with an envelope containing viral nucleocapsid. The nucleocapsid in CoVs are arranged in helical symmetry, which reflects an atypical attribute in Positive-sense RNA viruses (30). The electron micrographs of SARS-CoV-2 revealed a diverging spherical outline with some degree of pleomorphism, virion diameters varying from 60 to 140nm, and distinct spikes of 9 to 12nm, giving the virus the appearance of a solar corona (3). The CoV genome is arranged linearly as 5'-leader-UTR-replicase-structural genes (S-E-M-N) -3' UTR-poly(A) (32). Accessory genes, such as 3a/b , 4a/b , and the hemagglutinin-esterase gene (HE), are also seen intermingled with the structural genes (30). SARS-CoV-2 has also been found to be arranged similarly and encodes several accessory proteins, although it lacks the HE, which is characteristics of some Beta-coronaviruses (31). The Positive-sense genome of CoVs serves as the mRNA and is translated to poly-protein 1a/1ab (pp 1a/1ab) (33). A replication-transcription complex (RTC) is formed in double-membrane vesicles (DMVs) by non-structural proteins (nsps), encoded by the poly-proteins gene (34). Subsequently, the RTC synthesizes a nested set of subgenomic RNAs (sgRNAs) via discontinuous transcription (35).

A pandemic situation in the worldwide population, leading to disease outbreaks that have not been controlled to date, although extensive efforts are being put in place to counter this virus (25). This virus has been proposed to be designated/named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV), which determined the virus belongs to the Severe acute respiratory syndrome-related coronavirus category and found this virus is related to SARS-CoVs (26). SARS-CoV-2 is a member of the order Nidovirales, family Coronaviridae, subfamily Orthocoronavirinae, which is subdivided into four genera, viz., **Alpha-coronavirus, Beta-coronavirus, Gamma-coronavirus,** and **Delta-coronavirus** have evolved from bird and swine gene pools (24, 28, 29, 275).

Coronaviruses possess an unsegmented, single-stranded, positive-sense RNA genome of around 30 kb, enclosed by a 5'-cap and 3'-poly (A) tail (30). The genome of SARS-CoV-2 is 29,891 bp long, with a G+C content of 38% (31). These viruses are encircled with an envelope containing viral.

Some therapeutic options for treating COVID-19 showed efficacy in , in vitro studies; however, to date, these treatments have not undergone any randomized animal or human clinical trials, which limit their practical applicability in the current pandemic (7, 9,19-21).

The present comprehensive review describes the various features of SARS-CoV-2/ COVID-19 causing the current disease outbreaks and advance in diagnosis and developing vaccines and therapeutics. It also provides a brief comparison with the earlier SARS and MERS CoVs, the veterinary perspective of CoVs and this emerging novel pathogen, and an evaluation of the zoonotic potential of similar CoVs to provide feasible One Health strategies for the management of this fatal virus (22 - 367).

THE VIRUS (SARS-CoV-2)

Coronaviruses are Positive-sense RNA viruses having an extensive and promiscuous range of natural hosts and affect multiple systems (23, 24). Coronaviruses can cause clinical disease in humans that may extend from the common cold to more severe respiratory diseases like SARS and MERS (17 , 279). The recently emerging SARS-CoV-2 has wrought havoc in China and caused a pandemic situation in the worldwide population leading to

Furthermore, SARS-CoV-2 is genetically distinct from SARS-CoV (79% similarity) and MERS-CoV (nearly 50%) (17). COVID-19 is associated with afflictions of the lungs in all cases and generated characteristics chest computer tomography findings, such as the presence of multiple lesions in lung lobes that appear as dense, ground-glass opaque structures that occasionally coexist with consolidation shadows (18).

New targeted drugs, and prevention of further epidemics (13). The most common symptoms associated with COVID-19 are fever, cough, dyspnea, expectoration, headache, and myalgia or fatigue.

In contrast, less common signs at the time of hospital admission include diarrhea, Hemoptysis, and shortness of breath (14). Recently, individuals with asymptomatic infections were also suspected of transmitting infections, which further adds to the complexity of disease transmission dynamics in COVID-19 infections (1). Such efficient responses require in-depth knowledge regarding the virus, which currently is a novel agent; consequently, further studies are required.

Comparing the genome of SARS/SARS-like CoV revealed that the sequence coding for the spike protein, with a total length of 1,273 amino acids, showed 27 amino acid substitutions. Six of these substitutions are in the region of the receptor-binding domain (RBD), and another six substitutions are in the underpinning subdomain (SD) (16). Phylogenetic analysis have revealed that SARS-CoV-2 is closely related (88% similarity) to two SARS-like CoVs derived from bat SARS-like CoVs (bat-SL-CoVZC45 and bat-SL-CoVZXC21) (Fig. 1).

range of hosts, producing symptoms and diseases ranging from the common cold to severe and ultimately fatal illnesses, such as SARS, MERS, and presently, COVID-19. SARS-CoV-2 is considered one of the seven members of the CoV family that infect humans (3), and it belongs to the same lineage of CoVs that causes SARS; however, this novel virus is genetically distinct. Until 2020, six CoVs were known to infect humans, including human CoV 229E (HCoV-229E), HCoV-NL63, HCoV-OC43, HCoV-HKUI, SARS-CoV, and MERS-CoV have resulted in outbreaks with high mortality, others remain associated with mild upper-respiratory-tract illnesses (4).

Newly evolved CoVs pose a high threat to global public health. The current emergence of COVID-19 is the third CoV outbreaks in humans over the past 2 decades (5). It is no coincidence that Fan et al. Predicted potential SARs- or MERS-like CoV outbreaks in China following pathogen transmission from bats (6). COVID-19 emerged in China and spread rapidly throughout the country and, subsequently, to other countries. Due to the severity of this outbreak and the potential of spreading on an international scale, the WHO declared a global health emergency on **31 January 2020**; subsequently

on **11 March 2020**, they declared it a pandemic situation. At present, we are not in a position to effectively treat COVID-19, since neither approved vaccines nor specific antiviral drugs for treating human CoV infections are available (7 - 9). Most nations are currently making efforts to prevent the further spreading of this potentially deadly virus by implementing preventive and control strategies.

In domestic animals, infections with CoVs are associated with a broad spectrum of pathological conditions. Apart from infectious bronchitis virus, canine respiratory CoV, and mouse hepatitis virus, CoVs are predominantly associated with gastrointestinal disease (10). The emergence of novel CoVs may have become possible because of multiple CoVs being maintained in their natural host, which could have favored the probability of genetic recombination (10). High genetic diversity and the ability to infect multiple host species are a result of high-frequency mutations in CoVs, which occur due to the instability of RNA-dependent RNA polymerases along with higher rates of homologous RNA recombination (10, 11). Identifying the origin of SARS-CoV-2 and the pathogen's evolution will be helpful for disease surveillance (12).