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Coronavirus Disease 2019 – COVID-19

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Summary

In the past decades, several new diseases have emerged in new geographical areas, with pathogens including Ebola, Zika, Nipah, and coronaviruses (CoVs). Recently, a new type of viral infection has emerged in Wuhan City, China, and initial genomic sequencing data of this virus does not match with previously sequenced CoVs, suggesting a novel CoV strain (2019-nCoV), which has now been termed as severe acute respiratory syndrome CoV-2 (SARS-CoV-2). Although Coronavirus disease 2019 (COVID-19) is suspected to originate from an animal host (zoonotic origin) followed by human-to-human transmission, the possibility of other routes such as food-borne transmission should not be ruled out. Compared to diseases caused by previously known human CoVs, COVID-19 shows less severe pathogenesis but higher transmission competence, as is evident from the continuously increasing number of confirmed cases globally. Compared to other emerging viruses such as Ebola virus, avian H7N9, SARS-CoV, or MERS-CoV, SARS-CoV-2 has shown relatively low pathogenicity and moderate transmissibility. Codon usage studies suggest that this novel virus may have been transferred from an animal source such as bats. Early diagnosis by real-time PCR and next-generation sequencing has facilitated the identification of the pathogen at an early stage. Since, no antiviral drug or vaccine exists to treat or prevent SARS-CoV-2, potential therapeutic strategies that are currently being evaluated predominantly stem from previous experience with treating SARS-CoV, MERS-CoV, and other emerging viral diseases. In this review, we address epidemiological, diagnostic, clinical, and therapeutic aspects, including perspectives of vaccines and preventive measures that have already been globally recommended.

KEYWORDS: Emerging coronavirus; 2019-nCoV; SARS-CoV-2; COVID-19; diagnosis; vaccines; therapy; one health

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INTRODUCTION

Over the past two 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 syndromes (MERS) began to emerge in 2002 and 2012, respectively. At present, a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing the Coronavirus Disease 2019 (COVID-19), has emerged in late 2019, which has posed a global health threat with its 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) that was first identified in Wuhan City, Hubei Province, China, on December 12th, 2019. On February 11th, 2020, the World Health Organization (WHO) announced the official designation for this current CoV-associated disease to be "COVID-19", caused by the 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 range of hosts, producing symptoms and diseases ranging from a common cold to severe and ultimately fatal illnesses such as SARS, MERS, and, as of present, COVID-19. The SARS-CoV-2 (formerly 2019-nCoV) is considered as 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 include HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV, and MERS-CoV. Though 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 are thus posing a significant threat to global public health. Over the past two decades, the current emergence of COVID-19 is the third CoV outbreak in humans (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). The COVID-19 that emerged in China 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 January 31st, 2020. Subsequently, on March 11th, 2020, a pandemic situation was declared. 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 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, all other CoVs are predominantly associated with gastrointestinal diseases (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 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), development of new targeted drugs, and prevention of further epidemics (13). The most common symptoms associated with COVID-19 were fever, cough, dyspnea, expectoration, headache, and myalgia or fatigue.

In contrast, less common signs at the time of hospital admission included diarrhea, hemoptysis, and shortness of breath (14). Recently, individuals with asymptomatic infections were also suspected of potentially transmitting infections, which further add to the complexity of disease transmission dynamics in COVID-19 infections (1). The current status suggests that the COVID-19 outbreak in China may progress as a severe epidemic or even a pandemic if proper emergency response procedures or preventive and control measures are not applied (15). 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-CoV-2 with that of the closely related 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, and another six substitutions are in the underpinning subdomain (SD) (16). Phylogenetic analyses have revealed that the SARS-CoV-2 is closely related (88% similarity) to two SARS-like CoVs derived from bats (bat-SL-CoVZC45 and bat-SL-CoVZXC21). Furthermore, the SARS-CoV-2 is genetically distinct from SARS-CoV (79% similarity) and MERS-CoV (50%) (17). The COVID-19is associated with afflictions of the lungs in all cases and generated characteristic chest computer-tomography findings, such as the presence of multiple lesions in lung lobes that appear as dense ground-glass opaque structures and occasionally co-exist with consolidation shadows (18).

Some therapeutic options for treating COVID-19 have shown efficacy at *in vitro* studies; however, these treatments have to date 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 the COVID-19 (caused by the SARS-CoV-2) causing the current disease outbreaks, advances in diagnosis and developing vaccines and therapeutics, a brief comparison with the earlier SARS and MERS CoVs, the veterinary perspective of CoVs and this emerging novel pathogen as well as evaluate the zoonotic potential of similar coronaviruses and to provide feasible one health strategies for the management of this fatal virus (22-330).

THE VIRUS (SARS-CoV-2)

Coronaviruses are positive-sense RNA viruses having an extensive and promiscuous wide range of natural hosts and affect multiple systems (23, 24). Coronaviruses can cause clinical diseases in humans that may extend from the common cold to more severe respiratory diseases like SARS and MERS (17, 284). The recently emerging SARS-CoV-2 has caused havoc in China, and pandemic situation to the worldwide population, leading to current disease outbreaks that have not been controlled to date through high efforts are being put in to counter this virus. More recently, the WHO announced an official name for this disease as

COVID-19. For the time being, earlier, the WHO named this currently emerging virus as a 2019-novel coronavirus (2019-nCoV) and later the disease as COVID-19 (25). Later, this virus has been proposed to be designated/named as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV) *Coronaviridae* Study Group that determined the virus belongs to the existing species, *Severe acute respiratory syndrome-related coronavirus*, and found this virus related to SARS-CoVs (26). The SARS-CoV-2 is a member of the order *Nidovirales*, family *Coronaviridae*, sub-family *Orthocoronavirinae*, which is sub-divided into four genera, viz. *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus* (3, 27). The genera *Alphacoronavirus* and *Betacoronavirus* originate from bats, while the *Gammacoronavirus* and *Deltacoronavirus* have evolved from birds and swine gene pools (24, 28, 29, 280).

Coronaviruses possess an unsegmented, single-stranded (ss) 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 kb long, with a G + C content of 38% (31). These viruses are encircled with an envelope containing viral nucleocapsid. The nucleocapsids 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 divulging spherical outline with some degree of pleomorphism, virion diameter varying from 60 to 140 nm, and distinct spikes of 9 to 12 nm, giving the virus an appearance of a solar corona (3). The CoVs 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, hemagglutinin-esterase gene (HE) are also seen intermingled within the structural genes (30). The SARS-CoV-2 has also been found to be arranged similarly and encodes several accessory proteins, although it lacks the HE, which is characteristic of some *Betacoronaviruses* (31). The positive-sense genome of CoVs serves as mRNA and is translated to polyprotein 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 polyprotein (34). Subsequently, the RTC synthesizes a nested set of subgenomic RNAs (sgRNAs) via discontinuous transcription (35).

Based on molecular characterization, the SARS-CoV-2 is considered as a new *Betacoronavirus* belonging to the subgenus *Sarbecovirus* (3). Few other critical zoonotic viruses (MERS-related-CoV and SARS-related-CoV) also belong to the same genus. However, the SARS-CoV-2 was identified as a distinct virus based on the percent identity with other *Betacoronavirus;* conserved ORF 1ab is below 90% (3). An overall 80% nucleotide identity was observed between SARS-CoV-2 and original SARS-CoV along with 89% identity with ZC45 and ZXC21 SARS related CoVsof bats (2, 31, 36). In addition to this, 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 made known 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 possible role for this disease transmission to humans (31). Of note, the other two zoonotic CoVs (MERS-related-CoV and SARS-related-CoV) have also originated from bats (38, 39). Nevertheless, for SARS and MERS, civet cat and camels act as amplifier hosts, respectively (40, 41).

Coronaviruses genome and subgenome encode six open reading frames (ORFs) (31). The majority of the 5' end is occupied by ORF1a/b, which produces 16 nsps. The two polyproteins, pp1a and pp1ab, are initially produced from ORF1a/b by a -1 frameshift between ORF1a and ORF1b (32). The viral encoded proteases cleave polyproteins into individual nsps [Main protease (Mpro), chymotrypsin-like protease (3CLpro), and papain-like protease (PLPs)] (42). The SARS-CoV-2 also encodes these nsps, and their functions have been elucidated recently (31). Remarkably, a difference between SARS-CoV-2 and other CoVsis the identification of a novel short putative protein within ORF3 band a secreted protein with an alpha helix and beta-sheet with six strands encoded by the ORF8 (31).

Coronaviruses encode four major structural proteins, namely Spike (S), Membrane (M), Envelope (E), and Nucleocapsid (N), which are described in detail as below.

Spike glycoprotein 'S'

Coronavirus S protein is a large multifunctional class I viral transmembrane protein. The size of this abundant S protein varies from 1160 amino acids (IBV, Infectious Bronchitis Virus in poultry) to 1400 amino acids (FCoV, Feline Coronavirus) (43). It lies as 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 inside the cell through interaction with various host cellular receptors (44).

Furthermore, it acts as a critical factor for tissue tropism and the determination of host range (45). Notably, S protein is one of the vital immunodominant proteins of CoVs capable of inducing host immune response (45). The ectodomain in all CoVs S protein shows a similar domain organization, divided into two domains (43). The first one, S1, helps in host receptor binding while the latter one, S2, accounts for the fusion. The former (S1) is further divided into two subdomains, namely the N- terminal domain (NTD) and C- terminal domain (CTD). Both these subdomains act as the 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 trimeric S1 locates itself on top of the trimeric S2 stalk (45). Lately, the structural analyses of the S proteins of COVID-19have revealed 27 amino acid substitutions within a length of 1273 amino acid stretch (16). Among the six substitutions, located in the RBD (aa 357-528) while four substitutions in RBM at the CTD of the S1 domain (16). To the 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 is to know about how many differences would be required to change the host tropism. Sequence comparison revealed 17 non-synonymous changes in the early sequence of SARS-CoV-2 than the later isolates of SARS-CoV. The changes were found scattered over the genome of the virus with nine substitutions in the open reading frame (ORF) 1ab, ORF8 (4 substitutions), spike gene (3 substitutions), and ORF7a (single substitution) (4). Notably, the same non-synonymous changes were found in a familial cluster, indicating that the viral evolution might have happened during person-to-person transmission (4, 47). Such adaptive evolutions 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 mutations that occurs during subsequent human-to-human transmission is warranted.

M protein

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

E protein

The coronaviruses E protein is the most enigmatic and smallest among 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 viroporin (ion-channel) (53). Inactivation or absence of this protein is related to altered virulence of coronaviruses due to changes in morphology and tropism (54). The E protein consists of three domains, namely short hydrophilic amino-terminal, a large hydrophobic transmembrane domain, and an excellent 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 viral genome, facilitates M protein interaction needed during virion assembly, and enhances transcription efficiency of the virus (55, 56). It contains three highly conserved and distinct domains, namely an N-terminal domain (NTD), RNA-binding domain or a linker region (LKR), and a C-terminal domain (CTD) (57). The NTD binds with the 3' end of the viral genome, perhaps via electrostatic interactions, and is highly diverged both in length as well as sequence (58). The charged LKR is serine and arginine-rich and also known as SR (Serine and Arginine) domain (59). The LKR region is capable of direct interaction with *in vitro* RNA interaction and is also responsible for cell signaling (60, 61). It also modulates the antiviral response of the host by working as an antagonist for interferon and RNA interference (62). In comparison to SARS-CoV, the N protein of SARS-CoV-2 possess five amino acid mutations, where the two are in the intrinsically dispersed region (IDR, 25 & 26 positions), one each in the NTD (103 position), LKR (217 position) and CTD (334 position) (16).

NSPs and accessory proteins

Besides the important structural proteins, SARS-CoV-2genome contains 15 nsps, nsp1-nsp10 and nsp12-16 and 8 accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, and orf 14) (16). All these proteins play a specific role in viral replication (27). The difference in respect to the accessory proteins with SARS-CoV, SARS-CoV-2 does not contain 8a protein and

longer 8b, and shorter 3b proteins (16). The nsp7, nsp13, envelope, matrix, or accessory proteins p6 and 8b have not been detected with any amino acid substitutions in comparison to coronaviruses (16).

The virus structure of SARS-CoV-2 is depicted in **Fig. 1.**

SARS-CoV-2 spike glycoprotein gene analysis

i. Sequence percent similarity analysis

We assessed the nucleotide (NT) percent similarity using the MegAlign software program, where the similarity in between the current novel SARS-CoV-2 isolates was found in the range of 99.4 to 100 %. Among the other *Serbecovirus* CoV sequences, the novel SARS-CoV-2 sequences showed the highest similarity with Bat-SL-CoV with the NT percent identity ranges between 78.2 to 78.8%. Meanwhile, earlier reported SARS-CoVs showed 70.6 to 74.9 % similarity at NT levels with SARS-CoV-2. Further, the NT percent similarity was 55.4%, 45.5% to 47.9%, 46.2% to 46.6%, and 45.0% to 46.3% with the other four subgenera, namely *Hibecovirus*, *Nobecovirus*, *Merbecovirus*, and *Embecovirus*, respectively. The percent similarity index of current outbreak isolates signposts a close relationship of SARS-CoV-2 isolates to 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 supposition. Though, it was ascertained that the current novel SARS-CoV-2 isolates belong to the subgenus of *Sarbecovirus* falling inside the diverse range of *Betacoronaviruses.* Their possible ancestor was hypothesized to be of bat CoV strains wherein bats might have played a crucial part in harboring this class of viruses.

ii. Splits-Tree phylogeny analysis

In the unrooted phylogenetic tree of different betacoronaviruses based on the S protein, virus sequences from different subgenera grouped into separate clusters. SARS-CoV-2 sequences from Wuhan and other countries exhibited a close relationship and appeared in a single cluster (**Fig. 2**). The CoVs from the subgenus *Sarbecovirus* appeared jointly in the splits-tree and divided into three sub-clusters, namely SARS-CoV-2, Bat-SARS-like-CoV (Bat-SL-CoV) and SARS-CoVs (**Fig. 2**). In the case of other subgenera like *Merbecoviruses*, all the sequences grouped in a single cluster whereas in *Embecovirus* different species comprising of canine respiratory CoVs, bovine CoVs, equine CoVs, and human CoV strain (OC43) grouped inside a common cluster. Isolates in the subgenus *Nobecovorus* and *Hibecovirus* were found placed separately away from other reported SARS-CoVs but share a common origin from bats.

CURRENT WORLDWIDE SCENARIO OF SARS-CoV-2

This novel virus, SARS-CoV-2, comes under the subgenus *Sarbecovirus* of *Orthocoronavirinae* subfamily and is entirely different from the viruses responsible for MERS-CoV and SARS-CoV (3). The newly emerged SARS-CoV-2 comes under the group 2B coronavirus (2). The genome sequences of SARS-CoV-2 obtained from the patients share a 79.5% sequence similarity to that of SARS-CoV (63).

As on April 2, 2020, a total number of 8,96,450 confirmed cases of COVID-19 (with 45,526 deaths) were reported in 203 countries worldwide (WHO situation report, 73) (**Fig. 3**).

Initially, the epicenter of the SARS-CoV-2 pandemic was China, which reported a maximum of deaths associated with COVID-19, with 82,724 laboratory-confirmed cases with 3,327 deaths on April 2, 2020 (Fig. 4). The SARS-CoV-2 confirmed cases were reported in more than 203 countries apart from China till April 2, 2020 (Fig. 3, Fig. 4). (25, 64). Currently, all the continents in the world, except Antarctica, have COVID-19. For many weeks, Italy was the focus of concerns regarding the high number of cases, with 1,10,574 cases and 13,157 deaths (1°), but now, the United States is the country with the highest number of cases, 1,87,302 and 3,846 deaths. Spain, the third country with the highest number of cases, 1,02,136, is second in the number of deaths, 9,053. A John Hopkins University web platform has provided daily updates on the basic epidemiology of the COVID-19 outbreak (https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6) (238).

The COVID-19 has also been confirmed on a cruise ship named 'Diamond Princess' quarantined in the Japanese water territory (Port of Yokohama), as well as on other cruise ships in the world (239) (**Fig.3, Fig.4)**. The significant events occurred during the SARS-CoV-2/COVID-19 virus outbreak from 8th Dec. 2019 and till April 2, 2020, are presented as a timeline depiction in **Fig. 5.**

China at the beginning bears the majority of the burden associated with COVID-19 in the form of disease morbidity and mortality compared to other countries (65), but with time passing there was an evident displacement to Europe, particularly Italy and Spain, while the United States is now having the highest number of confirmed cases. The COVID-19 outbreak has also been associated with severe economic impact globally due to the sudden interruption of global trade and supply chains that forced the multinational companies to make hard decisions that lead 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, thus limiting the intensive care services only to a small proportion of critically ill patients (67). This might have also 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 one month (28 days) of the outbreak. This is impressively fast when 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 to the public. This bold move will play a crucial role in controlling the spread of this newly emerged novel coronavirus to other parts of the world (69). The possible origin of this novel virus 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, the seafood market in Wuhan, Hubei Province, China (**Fig. 6**). The restaurants of this market are famous for serving 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 might have occurred (71). Although the SARS-CoV-2 is suspected to be originating from an animal host (zoonotic origin) with the further human-to-human transmission (**Fig. 6**), the possibility of food-borne transmission should be ruled out with further investigations, since it is a latent possibility (1). Additionally, to that, other potential and expected routes would be associated with the transmission, as in other respiratory viruses, by direct contact, shaking contaminated hands, or by direct contact with contaminated surfaces (**Fig. 6**). Still, to be better defined, yet need to be answered if blood transfusion and organ transplantation (281), as well as transplacental and perinatal routes, would be possible for SARS-CoV-2 transmission (**Fig. 6**).

From experience with several outbreaks associated with known emerging viruses, higher pathogenicity of the virus is often associated with lower transmissibility. Compared to the emerging viruses like Ebola virus, Avian H7N9, SARS-CoV, and MERS-CoV, the SARS-CoV-2 have relatively lower pathogenicity and moderate transmissibility (15). The risk of death among the individuals infected with COVID-19 was calculated using infection fatality risk (IFR). The IFR was found to be in the range of 0.3% to 0.6% that is comparable to previously occurred Asian influenza pandemic (1957-1958) (73, 282).

Notably, the re-analysis of the COVID-19 pandemic curve from the initial cluster of cases pointed out a substantial human-to-human transmission. It is opined that the common SARS-CoV-2 exposure history at the Wuhan seafood market might have originated from the human-to-human transmission rather than animal-to-human transmission (74). Meanwhile, pointing out the zoonotic spillover in COVID-19 is too early to fully endorse (1). Following the initial infection, human-to-human transmission has been documented with a preliminary reproduction number (R_0) 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 (R_0) 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 R_0 value since there is a possibility of bias due to insufficient data. The higher R_0 value is indicative of the more significant potential of the SARS-CoV-2 transmission in a susceptible population. That 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 to be more nutritious (5).

After passing of struggling last four months from December 2019 to March 2020 now as COVID-19 conditions seem to be under control in China, again wet animal markets have been started, and people are enthusiastically buying bats, dogs, cats, birds, scorpions, badgers, rabbits, pangolins (scaly anteaters), minks, a soup made from palm civet, ostriches, hamsters, snapping turtles, ducks, fishes, Siamese crocodiles and other animal meat available there but without taking any precautions. The Chinese government is encouraging people to feel their routine back to normalcy. However this could be a risk when it is mentioned in the advisory to avoid contact with live-dead animals as for as possible as SARS-CoV-2 has shown zoonotic spillover, and we can not rule out the probability of any new mutation in the same virus being closely in contact with both animal and humans at the market (289). A few months back, China imposed a temporary ban on the sale of live-dead animals in wet markets.

However, now again, more than hundreds of such wet markets have been re-opened without optimizing any standard food safety and sanitation practices (291).

Being the largest populated country in the world and due to its domestic and international food exportation policies, now the whole world is in the face of menace, including China itself. Wet markets of live-dead animals do not maintain strict food hygienic practices, fresh blood splashes are present everywhere, on the floor, and the tabletop and such food customaries could encourage many pathogens to adapt, mutate and jump the species barrier. As a result, the whole world is suffering now with novel SARS-CoV-2 with more than 10,00,000 morbidity and approximately 50,000 mortality across the globe. There is an urgent need of rationale international campaign enforcing penalty against such unhealthy food practices of China to encourage the sellers regarding the upliftment of hygienic food practices or/else close the crude live-dead animal wet markets, and to modify its food policies in order to avoid further life and the economical threat of any new emerging or re-emerging pandemic due to animal-human close interaction (290).

This will increase the possibility of zoonotic disease transmission to humans. 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 considered as a source of infection to the other susceptible individuals (81). Both the asymptomatic and symptomatic patients secrete similar viral load, which indicates that the transmission capacity of asymptomatic or minimally symptomatic patients is very high. This reflects that the transmission of SARS-CoV-2 may occur 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 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 the SARS-CoV, reflecting it a controllable disease with moderate to high transmissibility (84).

Hence, the COVID-19 pandemic does not have any novel factors in it other than the new genetically unique pathogen and a new possible reservoir. The cause and the possible future outcome are just the repetitions of our previous interaction with these fatal coronaviruses. The only difference is the time of occurrence and the genetic distinctness of the pathogen involved. Mutations on the receptor-binding domain (RBD) of CoV allowed them to infect newer hosts, thereby expanding their reach to all corners of the world (85). This is a potential threat to both animal and public health. Advanced studies using Bayesian phylogeographic reconstruction identified the most probable origin of the SARS-CoV-2 is from 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 ACE-2 as an entry receptor while exhibiting similar RBD with SARS-CoV (17, 87, 256-257). Several countries have provided recommendations to their people traveling to China (88, 89). Compared to the previous coronavirus outbreak caused by SARS-CoV and MERS-CoV, the efficiency of human-to-human transmission in SARS-CoV-2 was thought to

be less. This was based on the assumption that the health workers were affected the least compared to the previous outbreaks of fatal coronaviruses (2). Super-spreading events are considered to be 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 occurs through contact with infected-asymptomatic or symptomatic individuals through human-to-human transmission (92). The occurrence of super-spreading events in the COVID-19 outbreak cannot be ruled out until its possibility is evaluated. Similar to SARS and MERS, the COVID-19 can also infect the lower respiratory tract with milder symptoms (27). The basic reproduction number of COVID-19 was found to be in the range of 2.8-3.3 based on real-time reports and 3.2-3.9 based on predicted infected cases (84).

CORONAVIRUSES (CoV) IN HUMANS – SARS, MERS, and COVID-19

Coronavirus infection in humans is commonly associated with mild to severe respiratory diseases that are characterized by high fever, severe inflammation, cough, and internal organs dysfunction that can even lead to death (92). Most of the identified coronaviruses cause common cold in humans. However, this changed when SARS-CoV was identified, paving the way for severe forms of the disease in humans (22). Our previous experience with the outbreaks of other coronaviruses like SARS and MERS suggests that the mode of transmission in COVID-19 can be mainly human-to-human transmission occurs through direct contact, droplets, and fomites (25). Recent studies on the aerosol and surface stability of SARS-CoV demonstrated that aerosol and fomite transmission of SARS-CoV-2 is feasible, as the virus can remain viable in aerosols for multiple hours and on surfaces up to days (259).

The immune response against Coronavirus is vital to control and get rid of the infection. However, maladjusted immune responses, as such, may contribute to the immunopathology of the disease resulting in impairment of pulmonary gas exchange. Understanding the interaction between CoVs and the host innate immune systems may throw light on our understanding of the lung inflammation associated with this infection (24).

SARS is a viral respiratory disease caused by a formerly unrecognized animal coronavirus that originated from the 'wet markets' in southern China after getting adapted to the human host, thereby enabling transmission between humans (90). The SARS outbreak reported in the year 2002-03 has identified 8098 confirmed cases with 774 total deaths (9.6%) (93). The outbreak has severely affected the Asia Pacific region, especially mainland China (94). Even though the case fatality rate of SARS-CoV-2 (COVID-19) is comparatively lower than SARS-CoV, there exists a severe concern linked to this outbreak due to its epidemiological similarity to influenza viruses (95, 284). This can fail the public health system, thus resulting in a pandemic (96).

The MERS is also a respiratory disease that was first reported in Saudi Arabia during the year 2012. The disease was found to have a case fatality rate of around 35% (97). The analysis of available datasets suggests that the incubation period of SARS-CoV-2, SARS-CoV, and MERS-CoV, is almost in the same range. The longest predicted incubation time of SARS-CoV-2 (COVID-19) is 14 days. Hence, suspected individuals are isolated for 14 days to avoid the risk of further spread (98). Even though a high similarity has been reported between the genome sequence of new coronavirus (SARS-CoV-2) and SARS-like CoVs, the

comparative analysis identified a furin-like cleavage site in the SARS-CoV-2 S protein that is missing in other SARS-like CoVs (99). The furin-like cleavage site is expected to playa role in the viral life cycle, disease pathogenicity, and might even act as a therapeutic target for furin inhibitors. The highly contagious nature of SARS-CoV-2 compared to its predecessors SARS might be the result of a stabilizing mutation that occurred in the endosome-associated-protein-like domain of nsp2 protein.

Similarly, the destabilizing mutation near to the phosphatase domain of nsp3 proteins in SARS-CoV-2 could put forward a potential mechanism that differentiates from SARS (100). Even though the case fatality rates reported in COVID-19 is meager compared to the previous SARS and MERS outbreaks, it has so far caused more death than the SARS and MERS combined (101). Possibly related to the viral pathogenesis is the recent finding of an 832-nt deletion in the ORF8, which appears to reduce replicative fitness of the virus and lead to attenuated phenotypes of SARS-CoV-2 (258).

Coronavirus is the most prominent example of a virus that has crossed the species barrier twice from wild animals to humans, SARS, and MERS (79, 102). The possibility of crossing the species barrier for the third time cannot be ruled out in the case of SARS-CoV-2 (COVID-19). Bats are recognized as the possible natural reservoir host of both SARS-CoV and MERS-CoV infection. In contrast, the possible intermediary host is Palm civet in SARS-CoV and Dromedary camel for MERS-CoV infection (102). Bats are considered as the ancestral hosts in both SARS and MERS (103). Bats are also considered as the reservoir host of human coronaviruses like HCoV-229E and HCoV-NL63 (104). In the case of COVID-19, there are two possibilities for primary transmission; either it can be transmitted through intermediate hosts similar to that of SARS and MERS or directly from bats (103). The emergence paradigm put forward in the SARS outbreak suggests that the SARS-CoV originated from the bats (reservoir host) and later jumped to civet (intermediate host) and incorporated changes within the receptor-binding domain (RBD) to improve binding to civet ACE2. This civet-adapted virus, during their subsequent exposure to humans at live-markets, promoted further adaptations that resulted in the epidemic strain (104). Transmission can also occur directly from the reservoir host to humans without RBD adaptations. The bat coronavirus that is currently in circulation maintains specific “poised” spike proteins that facilitate human infection without the requirement of any mutations or adaptations (105). Different species of bats carry a massive number of coronaviruses around the world (106) altogether.

The high plasticity in receptor usage, along with the feasibility of adaptive mutation and recombination, may result in frequent interspecies transmission of coronavirus from bats to animals and humans (106). The pathogenesis of most bat coronaviruses is unknown, as these viruses are not isolated and studied (4). In the year to the already available coronavirus hedgehog coronavirus HKU31, a *Betacoronavirus* has been identified from Amur hedgehogs in China. Study shows that hedgehogs are the reservoir of *Betacoronavirus*, and there is evidence of recombination (107).

The current scientific evidence available on MERS infection suggests that the significant reservoir host, as well as the animal source of MERS infection in humans, are the dromedary camels (97). The infected dromedary camels may not show any visible signs of infection, making it challenging to identify animals actively excreting MERS-CoV that has the potential to infect humans. However, they may shed MERS-CoV through milk, urine,

feces, nasal, and eye discharge and can also be found in the raw organs (108). In a study conducted to evaluate the susceptibility of animal species to MERS-CoV infection, llamas and pigs were found to be susceptible, indicating the possibility of MERS-CoV circulation in animal species other than dromedary camels (109).

Following the outbreak of SARS in China, SARS-CoV like viruses were isolated from Himalayan palm civets (*Paguma larvata*) and Raccoon dog (*Nyctereutes procyonoides*) found in a live-animal market in Guangdong, China. The animal isolates obtained from the live-animal market retained a 29-nucleotide sequence that was not found in most of the human isolates (78). These findings were critical in identifying the possibility of interspecies transmission in SARS-CoV. The higher diversity and prevalence of bat coronaviruses in this region compared to the previous reports indicate a host/pathogen coevolution. SARS-like coronaviruses have also been found circulating in the Chinese horseshoe bat (*Rhinolophus sinicus*) populations. The *in vitro* and *in vivo* studies carried out on the isolated virus confirmed that there is a potential risk for the re-emergence of SARS-CoV infection from the viruses that are currently being circulated in the bat population (105).

CLINICAL PATHOLOGY OF SARS-CoV-2 (COVID-19)

The disease caused by SARS-CoV-2 is also named as the Severe Specific Contagious Pneumonia (SSCP), Wuhan pneumonia, and recently named as Coronavirus Disease 2019, COVID-19, by WHO (110). Compared to the SARS-CoV, SARS-CoV-2 has less severe pathogenesis but has superior transmission competence that is evident from the continuously increasing confirmed cases (111). The incubation period of SARS-CoV-2 in familial clusters was found to be 3 to 6 days (112). The mean incubation period of COVID-19 was estimated to be 6.4 days and ranging from 2.1-11.1 days (113). Among the early affected people of 425 patients, 59 years was the median age group affected, of which more males were affected (114). Similar to SARS and MERS, the severity of this nCoV is high in age group people above 50 years (2, 115). Symptoms of COVID-19 include fever, cough, myalgia, or fatigue, less commonly headache, hemoptysis and diarrhea (116; 287). Compared to the patients infected with SARS-Cov-2 in Wuhan during the initial stages of the outbreak, only mild symptoms were noticed in those patients that are infected by human-to-human transmission (14).

The initial trends suggested that the mortality associated with COVID-19 is comparatively lesser than the previous outbreaks of SARS (101). The updates obtained from the countries like China, Japan, Thailand, and Korea indicate that the COVID-19 infection appears to be having relatively mild manifestations as compared with SARS and MERS (4). Regardless of the coronavirus type, immune cells like mast cells that are present in the submucosa of the respiratory tract and nasal cavity are considered as the primary barrier against this virus (92). Advanced in-depth analysis of the genome has identified 380 amino acid substitutions between the amino acid sequences of SARS-CoV-2 and the SARS/SARS-like coronaviruses. This difference in the amino acid sequence might have contributed to the difference in the pathogenic divergence of SARS-CoV-2 (16). Further researches are required to evaluate the possible difference in tropism, pathogenesis, and transmission of this novel agent associated with this change in the amino acid sequence. With the current outbreak of

COVID-19, there is an expectancy of a significant increase in the number of published studies about this emerging coronavirus, as occurred with SARS and MERS (117).

The 2019-n-CoV invades the lung parenchyma resulting in severe interstitial inflammation of the lungs. This will be evident on CT images as ground-glass opacity in the lungs. This lesion, even though initially, involves a single lobe but later expands to multiple lung lobes (118). The histological examination of lung biopsy samples obtained from COVID-19 infected patient showed diffuse alveolar damage, cellular fibromyxoid exudates, hyaline membrane formation, and desquamation of pneumocytes, indicative of acute respiratory distress syndrome (119). It has also been found that the SARS-CoV-2 infected patients often have lymphocytopenia along with/ without leukocyte abnormalities. The degree of lymphocytopenia gives an idea about the disease prognosis as it is found positively correlated with the disease severity (118). Pregnant women are considered to be having a higher risk of getting infected by COVID-19. The coronaviruses can cause adverse outcomes for the fetus, such as intrauterine growth restriction, spontaneous abortion, preterm delivery, and perinatal death.

Nevertheless, the possibility of intrauterine maternal-fetal transmission (vertical transmission) of CoVs is low, and it is not reported in either SARS or MERS (120). However, there has been concern regarding the impact of SARS-CoV-2/COVID-19 on the pregnancy.

Researchers have mentioned the probability of *in utero* transmission of novel SARS-CoV-2 from COVID-19 infected mothers to their neonates in China based upon the rise in IgM, IgG antibody levels and cytokine values in the blood obtained from newly borne infants immediately post-birth; however, reverse transcriptase-polymerase chain reaction (RT-PCR) did not confirm the presence of SARS-CoV-2 genetic material in the infants (288).

Recent studies show that at least, in some cases, preterm delivery and its consequences, are associated. Nevertheless, some cases have raised doubts regarding the possibility of vertical transmission (240-243).

The COVID-19 infection was associated with pneumonia, and some developed acute respiratory distress syndrome (ARDS). The blood biochemistry indexes such as albumin, lactate dehydrogenase, C-reactive protein, lymphocytes (%), and neutrophils (%) gives an idea about the disease severity in COVID-19 infection (121). During COVID-19, patients may present leukocytosis, leukopenia with lymphopenia (244), also hypoalbuminemia, an increase of LDH, AST, ALT, bilirubin, and especially D-dime (244). Middle-aged and elderly patients with primary chronic diseases, especially high blood pressure and diabetes, were found to be more susceptible to respiratory failure and thereby having poorer prognosis. Providing respiratory support at early stages improved the disease prognosis and facilitated recovery (18). The ARDS in COVID-19 is due to the occurrence of cytokine storms that results in exaggerated immune response, immune regulatory network imbalance, and, finally, can even lead to multiple organ failure (122). In addition to the exaggerated inflammatory response seen in patients with COVID-19 pneumonia, the bile duct epithelial cell-derived hepatocytes up-regulate the ACE2 expression in liver tissue by compensatory proliferation that might result in hepatic tissue injury (123).

CORONAVIRUSES (CoV) IN ANIMALS AND ZOONOTIC LINKS– A BRIEF VIEWPOINT

Coronavirus can cause disease in several species of domestic and wild animals, as well as humans (23). The different animal species that are infected with CoV include horses, camels, cattle, swine, dogs, cats, rodents, birds, ferrets, mink, bats, rabbits, snake, and several other wild animals (20, 30, 79, 93, 124, 125; Dhama et al., 2020). Coronavirus infection is associated with a wide variety of clinical manifestations ranging from enteritis in cows and pigs, upper respiratory disease in chickens, and potentially fatal respiratory infections in humans (30).

Among the CoVs genera, *Alphacoronavirus* and *Betacoronavirus* infect mammals. While *Gammacoronavirus* and *Deltacoronavirus* mainly infect birds, fishes, and sometimes also mammals (27, 29, 106). Several novel coronaviruses that come under the genus*Deltacoronavirus* have been discovered in the past from birds like Wigeon coronavirus HKU20, Bulbul coronavirus HKU11, Munia coronavirus HKU13, White-eye coronavirus HKU16, Night-heron coronavirus HKU19, Common moorhen coronavirus HKU21 and from pigs also (porcine coronavirus HKU15) (6, 29). Transmissible gastroenteritis virus (TGEV), porcine epidemic diarrhea virus (PEDV), and porcine hemagglutinating encephalomyelitis virus (PHEV) are some of the coronaviruses of swine. Among them, TGEV and PEDV cause severe gastroenteritis in young piglets leading to noteworthy morbidity and mortality. Infection with PHEV also cause enteric infection but can cause encephalitis due to its capability to infect the nervous system (30).

Bovine coronaviruses (BoCoVs) are known to infect several domestic and wild ruminants (126). BoCoVinflicts neonatal calf diarrhea, in adult cattle, leads to bloody diarrhea (winter dysentery), and respiratory disease complex (shipping fever) in cattle of all age groups (126). BoCoV-like viruses have been noted in humans suggesting its zoonotic potential as well (127). Feline enteric and feline infectious peritonitis (FIP) viruses are the two major feline CoVs (128). Where feline CoVs can affect GIT, abdominal cavity (peritonitis), respiratory tract, and CNS (128). Canines are also affected by CoVsand fall under different genera, namely canine enteric coronavirus in *Alphacoronavirus* and canine respiratory coronavirus in *Betaacoronavirus* affecting the enteric and respiratory tract, respectively (129,130). The infectious bronchitis virus (IBV) under *Gammacoronavirus* causes diseases of respiratory, urinary, and reproductive systems with substantial economic losses in chickens (131,132). In small laboratory animals, mouse hepatitis virus, rat sialodacryoadenitis coronavirus, guinea pig, and rabbit coronaviruses are the major CoVs associated with the disease manifestations like enteritis, hepatitis and respiratory infections (10, 133).

Swine acute diarrhea syndrome coronavirus (SADS-CoV) was first identified in suckling piglets with severe enteritis and belonged to the genus *Alphacoronavirus* (106). The outbreak was associated with considerable scale mortality of piglets (24,693 deaths) across four farms in China (134). The virus isolated from the piglets was almost identical and had a 95% genomic similarity with horseshoe bat (*Rhinolophus* sp.) coronavirus HKU2 suggesting bat origin of the pig virus (106, 134, 135). It is also imperative to note that the SADS-CoV outbreak started in Guangdong province, near to the location of the SARS pandemic origin (134). Before this outbreak, pigs were not known to be infected with bat-origin coronaviruses. This indicates that the bat-origin coronavirus might have jumped to pig by breaking the

species barrier. The next step of this "jump" might not end up in good since the pigs are considered as the mixing vessel for influenza A viruses due to their ability to get infected by both human and avian influenza A viruses (136).

Similarly, they can act as the mixing vessel for coronaviruses since they are in frequent contact with both humans and multiple wildlife species. Additionally, pigs are also found to be susceptible to infection with human SARS-CoV and MERS-CoV, thus making this scenario a nightmare (109, 137). It is only a matter of time that another zoonotic coronavirus results in an epidemic by 'jumping' the so-called species barrier (292).

The host spectrum of coronavirus got increased when a novel coronavirus named SW1 was identified in the liver tissue of the captive beluga whale (*Delphinapterus leucas*) (138). In the past decades, several novel coronaviruses were identified from different animal species. Bats can harbor these viruses without manifesting any clinical disease by persistently infected (30). They are the only mammals with capacity for a power-driven flight that enables them to migrate long distances compared to land mammals. Bats are distributed worldwide and also accounts for about a fifth of all the mammalian species (6). This makes them the ideal reservoir host, for many viral agents, and also the source of novel coronaviruses that are yet to be identified. It has become a necessity to study the diversity of coronavirus in the bat population to prevent future outbreaks that could jeopardize livestock and public health. The repeated outbreaks caused by bat origin coronaviruses calls for the development of efficient molecular surveillance strategies for studying the *Betacoronavirus* among animals (12), especially in the *Rhinolophus* bat family (86). Chinese bats had high commercial value since they are used in Traditional Chinese Medicine (TCM). Therefore, handling of bats for trading purposes poses considerable risk of transmitting zoonotic CoV epidemics (139).

Due to the possible role played by farm and wild animals in SARS-CoV-2 (COVID-19) infection, the WHO in their Novel Coronavirus (COVID-19) situation report has recommended to altogether avoid unprotected contact with both farm and wild animals (25). The live-animal markets, like the one in Guangdong, China, will provide a venue for the animal coronaviruses to amplify and to get transmitted to new hosts like humans (78). Such markets can be considered as a critical place for the origin of novel zoonotic diseases and have enormous public health significance in the event of an outbreak. Bats are the reservoirs for several viruses, and hence the role is bats in the present outbreak cannot be ruled out (140). In a qualitative study conducted for evaluating the zoonotic risk factors among the rural communities of southern China, the frequent human-animal interactions along with the low levels of environmental biosecurity were identified as the significant risks for the emergence of zoonotic disease in the local communities (141, 142).

The comprehensive sequence analysis performed on the SARS-CoV-2 RNA genome identified that the CoV from Wuhan is a recombinant virus of the bat coronavirus and another origin-unknown coronavirus. The recombination was found to have happened within the viral spike glycoprotein that recognizes the cell surface receptor. Further analysis of the genome based on codon usage identified that the snake is the most probable animal reservoir of SARS-CoV-2 (143). Contrary to these findings, another genome analysis proposed that the genome of SARS-CoV-2 is 96% identical to the bat coronavirus, reflecting its origin to be from the bats (63). The involvement of bat-derived materials in causing the current outbreak cannot be ruled out. High risk is involved in the production of bat-derived materials for TCM

practices involving the handling of wild bats. The use of bats for TCM practices will remain a severe risk for the occurrence of future zoonotic coronavirus epidemics (139).

Furthermore, the pangolins are endangered species of animals that harbor a wide variety of viruses, including coronaviruses (144). The coronavirus isolated from Malayan Pangolins (*Manis javanica*) showed a very high amino acid identity with COVID-19 at E (100%), M (98.2%), N (96.7%) and S genes (90.4%). The RBD of S protein in CoV isolated from Pangolin was almost identical (one amino acid difference) to that of SARS-CoV-2. A comparison of the genomes suggests the possibility of recombination between Pangolin-CoV-like viruses with that of the Bat-CoV-RaTG13-like virus. All this suggests pangolins' potential to act as the intermediate host of COVID-19 (145).

The human-wildlife interactions, even more in the context of climate change (142), are further considered high-risk and responsible for the emergence of SARS-CoV. The COVID-19 is also suspected of having a similar mode of origin. Hence, to prevent the occurrence of another zoonotic spillover (1), exhaustive coordinated efforts are needed to identify the high-risk pathogens harbored by the wild animal populations, conducting surveillance among the people who are susceptible for zoonotic spillover events (12) and to improve the biosecurity measures associated with wildlife trade (146). The serological surveillance study conducted in people living in the proximity to bat caves has earlier identified the serological evidence of SARS-related CoVs in humans. The people living at the wildlife-human interface, mainly in rural China, are regularly exposed to SARS-related coronaviruses (147). These findings will not have any significance until a significant outbreak occurs due to a virus-like SARS-CoV-2.

Further studies are required to identify the possible animal reservoirs of SARS-CoV-2, and the seasonal variation in the circulation of these viruses in the animal population. Research collaboration between human and animal health sectors is becoming a necessity to evaluate and identify the possible risk factors of transmission between animals and humans. Such collaboration will help to devise efficient strategies for the management of emerging zoonotic diseases (12).

DIAGNOSIS OF SARS-CoV-2 (COVID-19)

RNA tests can confirm the diagnosis of SARS-CoV-2 cases (COVID-19) with real-time RT-PCR or next-generation sequencing (148, 149, 245, 246). At present nucleic acid detection techniques like reverse transcription-polymerase chain reaction (RT-PCR) are considered as an effective method for confirming the diagnosis in clinical cases of COVID-19 (148). Several companies across the world are currently focusing on developing and marketing SARS-CoV-2 specific nucleic acid detection kits. Also, multiple laboratories are developing their own in-house RT-PCR. One of them is the SARS-CoV-2nucleic acid detection kit produced by Shuoshi Biotechnology (double fluorescence PCR method) (150). Up to March 30, 2020, the US Food and Drug Administration (FDA) has granted 22 *in vitro* diagnostics EUAs, including the RT-PCR Diagnostic Panel for universal detection of SARS-like betacoronaviruses and specific detection of SARS-CoV-2 that developed the US CDC (**Table 1**) (260, 261).

In a recent study, 95 full-length genomic sequences of SARAS-CoV-2 strains were retrieved from the National Center for Biotechnology Information and GISAID databases (262). These allow to establish the reference sequence by conducting multiple sequence alignment and phylogenetic analyses, and analyzed sequence variations along the SARS-CoV-2 genome. The homology among all viral strains was generally high, among them, 99.99% (99.91%-100%) at the nucleotide level and 99.99% (99.79%-100%) at the amino acid level. Although overall variation in ORF regions is low, 13 variation sites in 1a, 1b, S, 3a, M, 8, and N regions were identified, among which positions nt28144 in ORF 8 and nt8782 in ORF 1a showed mutation rate of 30.53% (29/95) and 29.47% (28/95), respectively. These findings suggested that there may be selective mutations in SARS-COV-2, and it is necessary to avoid certain regions when designing primers and probes. Establishment of the reference sequence for SARS-CoV-2 could benefit not only the biological study of this virus but also diagnosis, clinical monitoring, and intervention of SARS-CoV-2 infection in the future (262).

Nucleic acids of SARS-CoV-2can be detected from the samples (64), such as bronchoalveolar lavage fluid, sputum, nasal swabs, fiber bronchoscope brush biopsy, pharyngeal swabs, feces, blood, and urine, with different levels of diagnostic performances (**Table 2**) (80, 238, 245, 246). The viral loads of SARS-CoV-2 were measured using N-gene-specific quantitative RT-PCR assay in the throat swab and sputum samples collected from COVID-19 infected individuals. The result indicated that the viral load peaked at around 5–6 days following the onset of symptoms, and it ranged from 10^4 to 10^7 copies/mL during this time (151). In another study, the viral load was found to be higher in the nasal swabs rather than the throat swabs obtained from COVID-19 symptomatic patients (82). Although initially was thought that viral load would be associated with poor outcomes, some case reports have shown asymptomatic individuals with high viral loads (247). In a recent study, analyzing the viral load in nasal and throat swabs obtained from the 17 symptomatic patients concerning the day of onset of any symptoms, higher viral loads were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat. Authors suggest that the viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza and appears different from that seen in patients infected with SARS-CoV. In this study from China, the viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients (248). In South Korea, studies on viral load of SARS-CoV-2, suggests that their kinetics may be significantly different from that of previously reported other coronavirus infections such as SARS-CoV (255). Such findings are in concordance with reports that transmission may occur early in the course of infection and suggest that case detection and isolation may require strategies different from those required for the control of SARS-CoV. How the SARS-CoV-2 viral load correlates with culturable virus needs to be determined?. Identification of patients with few or no symptoms and with modest levels of detectable viral RNA in the oropharynx for at least five days suggests that we need better data to determine transmission dynamics and inform our screening practices (248).

The studies on viral load of SARS-CoV-2 show that this virus can actively replicate in the upper respiratory tract, and is shed for a prolonged time after symptoms end, including in stool. These findings suggest adjustments of current case definitions and re-evaluation of the prospects of outbreak containment (249). In some cases, the viral load studies of SARS-CoV-

2 have also been useful to recommend precautionary measures when handling certain samples, e.g., feces. In a recent study, from 17 confirmed cases of SARS-CoV-2 infection with available data (representing days 0–13 after onset), stool samples from nine (53%; days 0–11 after onset) were positive on RT-PCR analysis. Although the viral loads were less than those of respiratory samples (range 550 copies per mL to 1·21 × 105 copies per mL), this has essential biosafety implications (250).

The samples from 18 SARS-CoV-2 positive patients in Singapore who traveled from Wuhan to Singapore showed the presence of viral RNA in stool and whole blood but not in urine by real-time reverse transcriptase-polymerase chain reaction (293). Further, novel SARS-CoV-2 infections have been detected in a variety of clinical specimens like bronchoalveolar lavage fluid, sputum, nasal swabs, fibro-bronchoscope brush biopsy, pharyngeal swabs, feces, and blood (246).

The findings of SARS-CoV-2 on fecal samples have raised concerns and multiple questions. Although direct droplet transmission is an essential route of transmission, fecal excretion, environmental contamination, and fomites might contribute to viral transmission (251-254). Considering the evidence of fecal excretion for both SARS-CoV and MERS-CoV, and their ability to remain viable in conditions that could facilitate fecal-oral transmission, it is possible that SARS-CoV-2 could also be transmitted via this route. The possibility of fecal-oral transmission of SARS-CoV-2 has implications, especially in areas with poor sanitation. Coronaviruses are susceptible to antiseptics containing ethanol, and disinfectants containing chlorine or bleach (251-254). Strict precautions must be observed when handling the stools of patients infected with coronavirus, and sewage from hospitals should also be adequately disinfected. The importance of frequent and proper hand hygiene should be emphasized (251-254). Future research on the possibility of fecal-oral transmission of SARS-CoV-2 should include environmental studies to determine whether the virus remains viable in conditions that would favor such transmission. Study of the enteric involvement and viral excretion of SARS-CoV-2 in feces is required to investigate whether fecal concentrations of SARS-CoV-2 RNA correlate with the severity of the disease and presence or absence of gastrointestinal symptoms and whether fecal SARS-CoV-2 RNA can also be detected in the incubation or convalescence phases of COVID-19 (251-254).

The lower respiratory tract sampling techniques like bronchoalveolar lavage fluid (BALF) aspirate is considered to be the ideal clinical material than the throat swab due to its higher positive rate of the nucleic acid test (148). The diagnosis of COVID-19 can be made by using upper respiratory tract specimens collected using nasopharyngeal and oropharyngeal swabs. However, these techniques are associated with unnecessary risks to healthcare workers due to close contact with patients (152). Similarly, a single patient with a high viral load reported contaminating an entire endoscopy room by shedding the virus, which may remain viable for at least three days and considered as a great risk for uninfected patients and healthcare workers (294). Recently, it was found that the anal swabs gave more positive results compared to the oral swabs in the later stages of the infection (153). Hence, the clinicians have to be cautious while discharging any COVID-19 infected patient based on negative oral swab test results due to the possibility of fecal-oral transmission. Even though the viral loads in stool samples were found to be less than that of respiratory samples, strict precautionary measures have to be followed while handling the stool samples of COVID-19 suspected or infected patients (151). The children infected with SARS-CoV-2 experience only a mild form of illness and recovers immediately after treatment. It was recently found

that the stool samples of SARS-CoV-2 infected children that gave negative throat swab results were found to be positive within ten days of a negative result. That could result in the fecal-oral transmission of SARS-CoV-2 infections, especially in children (295). Hence, to prevent the fecal-oral transmission of SARS-CoV-2, infected COVID-19 patients should only be considered as negative when they are tested negative for SARS-CoV-2 in the stool sample.

A suspected case of COVID-19 infection is said to be confirmed if the respiratory tract aspirate or blood samples are tested positive for SARS-CoV-2 nucleic acid using RT-PCR or by the identification of SARS-CoV-2 genetic sequence in respiratory tract aspirate or blood samples tested (80). The patient will be confirmed as cured when two subsequent oral swabs results become negative (153). Recently, the live virus was detected in the self-collected saliva of patients infected with COVID-19. These findings were confirmative of using saliva as a non-invasive specimen for the diagnosis of COVID-19 infection in suspected individuals (152). It has also been observed that the initial screening of COVID-19 patients infected with RT-PCR may give negative results even if they have chest CT findings that are suggestive of infection. Hence, for the accurate diagnosis of COVID-19, a combination of repeated swab tests using RT-PCR and CT scanning is required to prevent the possibility of false-negative results during the disease screening (154). RT-PCR is the most widely used method of diagnosing COVID-19. However, it has some significant limitations in the clinical perspective since it will not give any idea regarding the disease progression. Droplet digital PCR (ddPCR) can be used for the quantification of viral load in the samples obtained from lower respiratory tracts. Hence, based on the viral load, we can quickly evaluate the progression of infection (296). In addition to all the above, sequencing and phylogenetics are critical in the correct identification and confirmation of the causing viral agent, and useful in order to establish relationships with previous isolates and sequences, as well to know, especially during an epidemic, the nucleotide, amino acid mutation as well molecular divergence. Rapid development and implementation of diagnostic tests against emerging novel diseases like COVID-19 pose a significant challenge due to the lack of enough resources and logistical limitations associated with an outbreak (155).

The SARS-CoV-2 infection can also be confirmed by isolation and culturing. The human airway epithelial cell culture was found to be useful in isolating the novel coronavirus, SARS-CoV-2 (3). The efficient control of an outbreak is dependent upon the rapid diagnosis of the disease. Recently, in response to the COVID-19 outbreak, 1-step quantitative real-time reverse-transcription PCR assays were developed that detect the ORF1b and N regions of the SARS-CoV-2 genome (156). That developed assay was found to achieve the rapid detection of SARS-CoV-2. Nucleic acid-based assays offer high accuracy in the diagnosis of SARS-CoV-2, but the current rate of spread limits its usage due to the lack of diagnostic assay kits. That will further result in the extensive transmission of COVID-19 since only a portion of suspected cases can be diagnosed. In such situations, conventional serological assays like ELISA that are specific to COVID-19 IgM and IgG antibodies can be used as a high-throughput alternative (149). At present, there is no diagnostic kit available for detecting the SARS-CoV-2 antibody (150). The specific antibody profiles of COVID-19 patients were analyzed and found that the IgM level lasted more than one month, indicating a prolonged stage of virus replication in SARS-CoV-2 infected patients. The IgG levels were found to increase only in the later stages of the disease. These findings indicate that the specific antibody profile of both SARS-CoV-2 and SARS-CoV was similar (330). These findings can be utilized for the development of specific diagnostic tests against COVID-19 and can be

used for rapid screening. Even though diagnostic test kits are already available that can detect the genetic sequences of SARS-CoV-2 (95), their availability is a concern as the number of COVID-19 cases are skyrocketing (155, 157) major problem associated with this diagnostic kit is that it works only when the test subject has an active infection thus limiting its use in the early stages of infection. Several labs around the world are currently on the quest for developing antibody-based diagnostic tests against SARS-CoV-2 (157).

Chest CT is an ideal diagnostic tool for identifying viral pneumonia. The sensitivity of chest CT is far more superior to the X-ray. The chest CT findings associated with COVID-19 infected patients include characteristic patchy infiltration that later progresses into ground-glass opacities (158). Early manifestations of COVID-19 pneumonia might not be evident in the X-ray chest radiography. In such situations, a chest CT examination can be performed as it is considered to be highly specific for COVID-19 pneumonia (118). Those patients having COVID-19 pneumonia will exhibit the typical ground-glass opacity in their chest CT images (154). The patients infected with COVID-19 had elevated plasma Angiotensin 2 levels. The level of Angiotensin 2 was found to be linearly associated with the viral load and lung injury, indicating its potential as a diagnostic biomarker (121). The chest CT imaging abnormalities associated with COVID-19 pneumonia have also been observed even in asymptomatic patients. These abnormalities progress from the initial focal unilateral to diffuse bilateral ground-glass opacities and will further progress to or co-exist with lung consolidations changes within 1-3 weeks (159). The role played by radiologists in the current scenario is very high. Radiologists can help in the early diagnosis of lung abnormalities associated with COVID-19 pneumonia. They can also help in the evaluation of disease severity, identifying its progression to acute respiratory distress syndrome, and the presence of secondary bacterial infections (160). Even though chest CT is considered an essential diagnostic tool for COVID-19, the extensive use of CT for screening purposes in suspected individuals might be associated with a disproportionate risk-benefit ratio due to increased radiation exposure as well as increased risk of cross-infection. Hence, the use of CT for early diagnosis of SARS-CoV-2 infection in high-risk groups should be done with great caution (297).

VACCINES, THERAPEUTICS, AND DRUGS

The recently emerged viruses, such as Zika, Ebola, and Nipah viruses and their high threats to humans, have paved race in exploring of designing and developing advanced vaccines, prophylactics, therapeutics, and drugs regimens to counter emergency viruses (161-163, 285). Several attempts are being made to design and develop vaccines against coronavirus infection, mostly by targeting the Spike glycoprotein. Nevertheless, owing to the extensive diversity in antigenic variants, cross-protection rendered by the vaccines is significantly limited even within the strains of a phylogenetic sub-cluster (104). Due to the lack of effective antiviral therapy and vaccines in the present scenario, we have to rely exclusively on enforcing infection control measures to minimize the risk of possible nosocomial transmission (68). Recently, the receptor for SARS-CoV-2 was confirmed as the human angiotensin-converting enzyme 2 (hACE2), and the virus was found to enter the host cell mainly through endocytosis. It was also found that the major components that have a critical role in the viral entry include PIKfyve, TPC2, and cathepsin L. These findings are critical since the components described above might act as a potential candidate for vaccines or therapeutic drugs against SARS-CoV-2 (298).

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The majority of the therapeutic options and strategies that we are evaluating in SARS-CoV-2 (COVID-19) are taken from our previous experiences in treating SARS-CoV, MERS-CoV, and other emerging viral diseases. Several therapeutic and preventive strategies, including vaccines, immunotherapeutics, and antiviral drugs, have been explored against the previous coronavirus outbreaks caused by SARS-CoV and MERS-CoV (8, 104, 164-167). These valuable options have already been evaluated for their potency, efficacy, and safety along with several other ongoing types of research will fuel our search for ideal therapeutic agent against COVID-19 (7, 9, 19, 21, 36). The main reason for the lack of approved and commercially available vaccines or therapeutic agents against the previous coronaviruses like SARS-CoV and MERS-CoV might be due to the lack of interest among the pharmaceutical companies (19). These are outbreak scenarios: the demand for drugs or vaccines lasts for a period until the outbreak lasts. The number of people affected will also be a small proportion of the global drug and vaccine market. So, by the time a new drug or vaccine is developed, there would not be any patients for clinical trials, and also there would not be any market for the newly discovered drugs to be sold. At present, there is no vaccine or therapeutic drugs available for treating COVID-19 infection.

Vaccines

The S protein plays a significant role in the induction of protective immunity against SARS-CoV by mediating T-cell responses and neutralizing-antibody production (168). In the past few decades, we have seen several attempts to develop a vaccine against human coronaviruses by using S protein as the target (168, 169). However, the developed vaccines have minimal application even among closely related strains of the virus due to a lack of cross-protection. That is mainly because of the extensive diversity existing among the different antigenic variants of the virus (104). The contributions of the structural proteins like a spike (S), matrix (M), small envelope (E), and nucleocapsid (N) proteins of SARS-CoV to induce protective immunity has been evaluated by expressing them in a recombinant parainfluenza virus type 3 vector called BHPIV3. Of the note, the result was conclusive that the expression of M, E, or N proteins without the presence of S protein would not confer any detectable protection with the absence of detectable serum SARS-CoV-neutralizing antibodies (170). Antigenic determinant sites present over S and N structural proteins of SARS-CoV-2 can be well explored as a suitable vaccine candidate (299). In the Asian population, S, E, M, and N proteins of novel-SARS-CoV-2 can be tested for developing subunit vaccines against COVID-19 (300).

Identification of the immunodominant region among the subunits and domains of S protein is critical while developing an effective vaccine against the coronavirus. The C-terminal domain of the S1 subunit is considered as the immunodominant region of the porcine deltacoronavirus S protein (171). Similarly, further studies are required to determine the immunodominant regions of SARS-CoV-2 for facilitating vaccine development.

However, our previous attempts to develop a universal vaccine that is effective against both SARS-CoV and MERS-CoV based on T cell epitopes similarity pointed out the possibility of cross-reactivity among coronaviruses (172). That can be made possible by selected potential vaccine targets that are common to both the viruses. The SARS-CoV-2 is found to be closely related to the SARS-CoV (173,174). Hence, the knowledge and

understanding of the S protein-based vaccine development in SARS-CoV will help to identify potential S protein vaccine candidates in SARS-CoV-2. Therefore, vaccine strategies based on the whole S protein, S protein subunits, or specific potential epitopes of S protein appear most promising vaccine candidates against coronaviruses shortly. The RBD of the S1 subunit of S protein has a superior capacity to induce neutralizing antibodies. This property of RBD can be utilized for developing effective SARS-CoV vaccines either by using RBD containing recombinant proteins or recombinant vectors that encode RBD (175). Hence, the superior genetic similarity existing between SARS-CoV-2 and SARS-CoV can be utilized to repurpose vaccines that have proven *in vitro* efficacy against SARS-CoV to be utilized for SARS-CoV-2. The possibility of cross-protection in COVID-19 was evaluated by comparing the S protein sequences of SARS-CoV-2with that of SARS-CoV. The comparative analysis confirmed that the variable residues were found concentrated on the S1 subunit of S protein, an important vaccine target of the virus (150). Hence, the possibility of SARS-CoV specific neutralizing antibodies providing cross-protection to COVID-19 might be less. Further genetic analysis is required between COVID-19 and different strains of SARS-CoV and SARS-like (SL) coronaviruses to evaluate the possibility of repurposed vaccines against COVID-19. This strategy will be helpful in the scenario of an outbreak since much time can be saved because preliminary evaluation, including *in vitro* studies, would be already over in such vaccine candidates.

Identifying epitopes that have the potential to become a vaccine candidate is critical to developing an effective vaccine against COVID-19. Immuno-informatics approach has been used for the identification of essential epitopes of cytotoxic T lymphocyte and B cell from surface glycoprotein of SARS-CoV-2. Recently, a few epitopes have been recognized from the SARS-CoV-2surface glycoprotein. The selected epitopes explored targeting molecular dynamic simulations evaluating their interaction with corresponding MHC class I molecules. They potentially induce immune responses (176). The recombinant vaccine can be designed by using rabies virus (RV) as a viral vector. The RV can be made to express MERS-CoV S1 protein on its surface so that an immune response is induced against MERS-CoV. The RV vector-based vaccines against MERS-CoV can induce faster antibody response as well as higher degrees of cellular immunity compared to the Gram-positive enhancer matrix (GEM) particles vector-based vaccine. However, the latter can induce a very higher antibody response at lower doses (167). Hence, the degree of humoral and cellular immune response produced by such vaccines depends upon the vector used.

Dual vaccines are getting more popular recently. Among them, the rabies virus-based vectored vaccine platform is used to develop vaccines against emerging infectious diseases. The dual vaccine developed from inactivated rabies virus particles that express the MERS-CoV S1 domain of S protein was found to induce immune responses against both MERS-CoV and rabies virus. The vaccinated mice were found to be completely protected from the MERS-CoV challenge (169). The intranasal administration of the recombinant adenovirus-based vaccine in BALB/c mice was found to induce long-lasting neutralizing immunity against MERS spike pseudotyped virus characterized by the induction of systemic IgG, secretory IgA, and lung resident memory T cell responses (177). Immuno-informatics methods are employed for the genome-wide screening of potential vaccine targets among the different immunogens of MERS-CoV (178). The N protein, as well as the potential B cell epitopes of the E protein of the MERS-CoV, have been suggested as probable

immunoprotective targets inducing both T-cell and neutralizing antibody responses (178, 179).

The collaborative effort of the scientists of Rocky Mountain Laboratories and Oxford University is on the way for designing a chimpanzee adenovirus-vectored vaccine candidate to counter COVID-19 (180). The Coalition for Epidemic Preparedness Innovations (CEPI) has initiated three programs to develop SARS-CoV-2 vaccines (181). CEPI has a collaborative project with Inovio for designing the MERS CoV DNA vaccine that could potentiate effective immunity. CEPI and the University of Queensland are designing the molecular clamp vaccine platform for MERS-CoV and other pathogens, which could assist an easier recognition of antigens by the immune system (181). CEPI has also funded Moderna to develop a vaccine against COVID-19 in collaboration with Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases (NIAID), a part of National Institutes of Health (NIH) (182). By employing mRNA vaccine platform technology, a vaccine candidate expressing SARS-CoV-2 spike protein is expected to go through clinical testing in the coming months (180). On March 16th, Jennifer Haller became the first person outside of China to receive an experimental vaccine that was developed by Moderna against the pandemic virus. Moderna, along with China's CanSino Biologics, became the first research group that launched small clinical trials of vaccines against COVID-19. The study was conducted to evaluate the vaccine's safety and ability to trigger immune responses (301).

Scientists from all over the world are trying hard to develop working vaccines with robust protective immunity against COVID-19. Vaccine candidates like mRNA-1273 SARS-CoV-2 Vaccine, INO-4800 DNA coronavirus vaccine and Adenovirus type 5 vector vaccine candidate (Ad5-nCoV) are few examples under Phase-I clinical trials, while Self-amplifying RNA vaccine, Oral recombinant COVID-19 vaccine, BNT162, Plant-based COVID-19 vaccine and Ii-Key peptide COVID-19 vaccine are under preclinical trial mode (302). Similarly, the WHO, on its official website, has mentioned a detailed list of COVID-19 vaccine agents that are under consideration. Different phases of trials like live attenuated virus vaccines, formaldehyde alum inactivated vaccine, Adenovirus type 5 vector vaccine, LNP-encapsulated mRNA, DNA plasmid vaccine, S protein, S-trimer, Ii-Key peptide as subunit protein vaccine, among others (303).

Therapeutics and drugs

There is no currently licensed specific anti-viral treatment for the MERS and SARS-CoV infections, and the primary measure in the clinical management is focused on alleviating clinical symptoms and supportive cares (183-186). The first therapeutic drugs that might be effective in managing COVID-19 include remdesivir, lopinavir/ritonavir alone or in combination with interferon-β, convalescent plasma, and mAbs (187, 286). Nevertheless, before utilizing these drugs for COVID-19 pneumonia patients, efficacy and safety studies should be conducted by further clinical trials. Although a controlled trial of ritonavir-boosted lopinavir and interferon-alpha 2b therapy has been registered for hospitalized patients with COVID-19 (ChiCTR2000029308) (188). Besides, the use of hydroxychloroquine and tocilizumab and their potential role in modulating inflammatory response in the lungs, in addition to the potential of antiviral of the first, has been proposed and discussed in multiple papers, but so far, not available good-quality clinical trials have been published (263-277). Shortly, evidence will be available regarding the use of these drugs. Recently, also, a clinical

trial was published showing the comparison of lopinavir/ritonavir versus standard case but showed that in hospitalized adult patients with severe COVID-19, no benefit was observed with lopinavir-ritonavir treatment beyond standard care (278).

The guidance to the control of the COVID-19 infection might be based on the existing measures for MERS and SARS and with some further precautions because of the widely unknown nature of this new coronavirus (36, 189). Currently, the primary treatment strategy, such as mechanical ventilation, ICU admission, and symptomatic and supportive care, are commonly recommended for severe cases. Furthermore, RNA synthesis inhibitors (like 3TC, TDF), remdesivir, neuraminidase inhibitors, peptide (EK1), anti-inflammatory drugs, abidol, Chinese traditional medicine, such as Lianhuaqingwen and ShuFengJieDu Capsules, could be the promising drug treatment for COVID-19 (7). However, further clinical trials are required for confirming their safety and efficacy in managing the COVID-19 infection. The major limiting factor in the quest for identifying an ideal vaccine or therapeutic agent is time. It may take months to even several years for researchers to develop, produce, standardize, evaluate, approve, and commercialize specific therapeutic agents against COVID-19 infection. Hence, our current efforts should be directed towards identifying and evaluating therapeutic drugs/immunotherapeutic agents that have proven efficacy against viral agents that are similar toCOVID-19. The time required for a drug discovery program to develop, evaluate, and obtain approval for a new potent antiviral agent against COVID-19 should take more than ten years (9). In the present scenario, the development of a new therapeutic agent against COVID-19 is not a feasible option for the available time.

The COVID-19 patients showing severe signs are treated symptomatically along with oxygen therapy. In cases where the patients progress to respiratory failure and become refractory to oxygen therapy, mechanical ventilation is initiated. The COVID-19 induced septic shock can be managed by providing adequate hemodynamic support (304). Several classes of drugs are currently being evaluated for their potential therapeutic action against SARS-CoV-2. However, therapeutic agents that are having anti-SARS-CoV-2 activity can be broadly classified into three categories; drugs that block the entry of the virus into the host cell, drugs that block viral replication as well as its survival within the host cell, and drugs that attenuate the exaggerated host immune response (305). Inflammatory cytokine storm is commonly seen in critically ill COVID-19 patients. Hence, they may be benefited from the use of timely anti-inflammation treatment. Anti-inflammatory therapy using drug-like glucocorticoids, cytokine inhibitors, JAK inhibitors, and chloroquine/hydroxychloroquine should be done only after analyzing the risk and benefit ratio in COVID-19 patients (306). There have not been any studies regarding the use of non-steroidal anti-inflammatory drugs (NSAID) among COVID-19 infected patients. However, reasonable pieces of evidence are available that link NSAID uses with the occurrence of respiratory and cardiovascular adverse effects. Hence, as a cautionary approach, it is better to recommend the use of NSAIDs as the first-line option for managing COVID-19 symptoms (307). The use of corticosteroids in COVID-19 patients is still a matter of controversy and requires further systematic clinical studies. The guideline that was put forward to manage critically ill adults with COVID-19 suggests the use of systemic corticosteroids in mechanically ventilated adults with acute respiratory distress syndrome (ARDS) (308). The generalized use of corticosteroids is not indicated in COVID-19 since there are some concerns associated with the use of corticosteroids in viral pneumonia. Stem cell therapy using mesenchymal stem cells (MSCs)

is another promising strategy that can be used in the clinical cases of COVID-19 owing to their potential immunomodulatory capacity. It may have a beneficial role in attenuating the cytokine storm that is observed in the severe cases of SARS-CoV-2 infection, thereby reducing the mortality. Among the different types of MSCs, expanded umbilical cord mesenchymal stem cells can be considered as a potential therapeutic agent that requires further validation for managing critically ill COVID-19 patients (309).

Another option is to repurpose broadly acting anti-viral drugs that have already been used for other viral infections. Such drugs have the advantage of easy availability, known pharmacokinetic and pharmacodynamic properties, solubility, stability, side effects, and also well-established dosing regimens (9). Repurposed drugs are potential therapeutic options for the management of coronavirus infections. The repurposed drugs like lopinavir/ritonavir and interferon-1β possess in vitro anti-MERS-CoV activity. The *in vivo* study conducted in common marmosets (non-human primate model) identified that the animals treated with lopinavir/ritonavir and interferon-beta had better outcomes compared to the untreated animals (190). The combination of lopinavir-ritonavir and interferon-beta is currently being evaluated for the treatment of MERS in humans (MIRACLE trial) (191). The same two protease inhibitors lopinavir and ritonavir, when combined with another drug ribavirin, were found to be associated with favorable clinical response in SARS patients indicating therapeutic efficacy (165). However, in the present scenario, due to the lack of specific therapeutic agents against SARS-CoV-2, the hospitalized patients confirmed for the disease will receive supportive care like oxygen therapy and fluid therapy along with the antibiotic therapy for managing secondary bacterial infections (192).Patients with novel coronavirus or COVID-19 pneumonia who are mechanically ventilated often require sedatives, analgesics, and even muscle relaxation drugs to prevent ventilator-related lung injury associated with human-machine incoordination (122). The result obtained from a clinical study containing four patients infected with COVID-19 claimed that combination therapy using lopinavir/ritonavir, arbidol, and ShufengJiedu Capsule (Traditional Chinese medicine) was found to be effective in managing COVID-19 pneumonia (193). It is difficult to evaluate the therapeutic potential of a drug or a combination of drugs for managing a disease based on such a low and limited sample size. Before choosing the ideal therapeutic agent for the management of COVID-19, randomized clinical control studies should be performed with a sufficient study population.

Antiviral drugs

Several classes of routinely used antiviral drugs like oseltamivir (neuraminidase inhibitors), acyclovir, ganciclovir, and ribavirin does not have any effect on COVID-19 and hence not recommended (187). Oral administration of neuraminidase inhibitors such as oseltamivir has been widely used as an experimental drug for COVID-19 suspected cases in the hospitals of China even though there is no evidence of its efficacy (7). Recently, the *in vitro* antiviral efficacy of FAD-approved drugs such as ribavirin, penciclovir, nitazoxanide, nafamostat, and chloroquine were compared with that of the two broad-spectrum antiviral drugs remdesivir and favipiravir against the SARS-CoV-2. Among the evaluated drugs, both remdesivir and chloroquine were found to be highly effective in controlling COVID-19 infection *in vitro* (194). The study also pointed out that the three nucleoside analogs such as ribavirin, penciclovir, and favipiravir may not have significant *in vivo* antiviral effects against SARS-CoV-2 since higher concentrations were required to reduce the viral infection *in vitro*.

Both remdesivir and chloroquine are currently being used in humans for the treatment of other diseases. They also have a well-defined safety profile in human beings. Hence, such drugs can be used for evaluating their efficacy in patients of novel coronavirus infections.

Although no antiviral drugs have been approved for the treatment, several therapeutic agents such as lopinavir/ritonavir, chloroquine, and hydroxychloroquine are being proposed for the clinical management of COVID-19 (304). The molecular docking study conducted in the RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 using different commercially available anti-polymerase drugs identified that the drugs such as Ribavirin, Remdesivir, Galidesivir, Tenofovir, and Sofosbuvir were found to bind RdRp tightly indicating a great potential to be used as a therapeutic agent against COVID-19 (310). The broad-spectrum antiviral drug that was developed in the USA, Tilorone dihydrochloride (Tilorone), has been previously found to possess potent antiviral activity against MERS, Marburg, Ebola, and Chikungunya (311). Even though it had broad-spectrum activity, it was neglected for an extended period. Tilorone is another antiviral drug that might have activity against SARS-CoV-2.

Remdesivir, a novel nucleotide analog prodrug, was developed for the treatment of Ebola virus disease (EVD), and it was also found to inhibit replication of SARS-CoV and MERS-CoV in primary human airway epithelial cell culture system (195). Recently, *in vitro* study has proven that remdesivir has superior antiviral activity than lopinavir and ritonavir. Further, *in vivo* studies conducted in mice also identified that treatment with remdesivir improved pulmonary function and reduced viral loads and lung pathology both in prophylactic and therapeutic regimens compared to lopinavir/ritonavir-IFN-γ treatment in MERS-CoV infection (8). Remdesivir also inhibits a diverse range of coronaviruses, including circulating human CoV, zoonotic bat CoV, and pre-pandemic zoonotic CoV (195). Remdesivir is also considered as the only therapeutic drug that significantly reduces pulmonary pathology (8). All these findings indicate that the drug remdesivir has to be further evaluated for its efficacy in the treatment of COVID-19 infection in humans. The broad-spectrum activity exhibited by remdesivir will help control the spread of disease in the event of a new coronavirus outbreak.

Chloroquine is an anti-malarial drug known to possess antiviral activity due to its ability to block virus-cell fusion by raising the endosomal pH necessary for fusion. It also interferes with the virus-receptor binding by interfering with the terminal glycosylation of SARS-CoV cellular receptors, angiotensin-converting enzyme 2 (ACE2) (196). In a recent multicentre clinical trial that was conducted in China, chloroquine phosphate was found to exhibit both efficacy and safety in the therapeutic management of SARS-CoV-2 associated pneumonia (197). This drug is already included in the treatment guidelines issued by the National Health Commission of the People's Republic of China. The preliminary clinical trials using hydroxychloroquine, another aminoquinoline drug, gave promising results. The COVID-19 patients received 600 mg of hydroxychloroquine daily along with azithromycin as a single-arm protocol. This protocol was found to be associated with a significant reduction in the viral load. Finally, it resulted in a complete cure (275) —however, the study comprised a small population and hence the possibility of a misinterpretation. However, in another case study, the authors had raised concerns over the efficacy of hydroxychloroquine-azithromycin in the treatment of COVID-19 patients since no observable effect was seen when they were used. In some cases, the treatment was discontinued due to the prolongation of the QT

interval (312). Hence further randomized clinical trials are required before concluding this matter.

Recently, another FDA approved drug ivermectin was found to inhibit the in vitro replication of SARS-CoV-2. The findings from this study indicate that a single treatment of this drug was able to induce a ~5000-fold reduction in the viral RNA at 48h in cell culture. (313). In the coming days, further, *in vivo* studies will give an insight into the clinical utility of this wonder drug.

Nafamostat is a potent inhibitor of MERS-CoV that acts by preventing membrane fusion. Nevertheless, it does not have any sorts of inhibitory action against SARS-CoV-2infection (194). Recently, several newly synthesized halogenated triazole compounds were evaluated using fluorescence resonance energy transfer (FRET) based helicase assays for their ability to inhibit helicase activity.

Among the evaluated compounds, 4-(cyclopent-1-en-3-ylamino)-5-(2-(4-iodophenyl)hydrazinyl)-4H-1,2,4-triazole-3-thiol and 4-(cyclopent-1-en-3-ylamino)-5-[2-(4-chlorophenyl)hydrazinyl]-4H-1,2,4-triazole-3-thiolwere found to be the most potent. These compounds were used for in silico studies, and molecular docking was accomplished into the active binding site of MERS-CoV helicase nsp13 (21). Further studies are required for evaluating the therapeutic potential of these newly identified compounds in the management of COVID-19 infection.

Passive immunization/ Antibody therapy/ Monoclonal antibody (mAb)

Monoclonal antibodies (mAbs) may be helpful in the intervention of disease in CoV exposed individuals. Patients recovering from SARS showed robust neutralizing antibodies against this CoV infection (164). A set of mAbs functionally targetting the specific domains of the MERS-CoV S protein, including six specific epitope groups interacting with receptor binding, membrane fusion, and sialic acid-binding sites which constitute vital entry functions of S protein (198, 199). Passive immunization with poorly and potently neutralizing antibodies provided substantial protection in mice after a lethal challenge with MERS-CoV. Such antibodies may play a crucial role in enhancing humoral protection against the emerging CoVs by targeting important epitopes and roles of the S protein. The cross-neutralization ability of SARS-CoV RBD-specific neutralizing mAbs considerably relies on the similarity between their RBDs, therefore SARS-CoV RBD-specific antibodies could cross-neutralized SARS-like (SL) CoVs, i.e., bat-SL-CoV strain WIV1 (RBD with eight amino acids-difference to SARS-CoV), but not bat-SL-CoV strain SHC014 (24 amino acids-difference) (200).

Suitable RBD-specific mAbs can be identified by a comparative analysis of COVID-19 RBD with that of SARS-CoV, and cross-neutralizing SARS-CoV RBD-specific mAbs could be explored for their effectiveness against COVID-19 and further need to be assessed clinically. The U.S. Biotech Regeneron is attempting to recognize mAbs specific and potent to combat COVID-19. A perfect therapeutic option suggested for SARS-CoV-2 (COVID-19) is the combination therapy comprising of mAbs and the drug remdesivir (COVID-19) (201). The SARS-CoV specific human monoclonal antibody CR3022 is found to bind with SARS-CoV-2 RBD, indicating its potential to develop a therapeutic agent in the management of

COVID-19. It can be either used alone or in combination with other effective neutralizing antibodies for the treatment and prevention of COVID-19 (202). It was further observed that the other SARS-CoV-specific neutralizing antibodies like m396 and CR3014 failed to bind the S protein of SARS-CoV-2, indicating that a particular level of similarity is mandatory between the RBD's of SARS-CoV and SARS-CoV-2 for the cross-reactivity to occur.

Further, assessment is necessary before confirming the effectiveness of such combination therapy. Besides, the post-procedure risk management program should not be neglected in order to prevent further community and nosocomial spread of COVID-19 (314). Development of broad-spectrum inhibitors against the often human coronaviral pathogens will help to facilitate clinical trials on the effectiveness of such inhibitors against the endemic and other emerging coronaviruses (203). A promising animal study revealed the protective effect of passive immunotherapy with immune serum from MERS-immune camels on mice infected with MERS-CoV (204). Passive immunotherapy using convalescent plasma is another strategy that can be used for treating COVID-19 infected critically ill patients (205).

Inhibition of virus replication can be achieved by exploiting fully human antibodies (human single-chain antibodies; HuscFvs) or humanized-nanobodies (single-domain antibodies, sdAb, VH/VHH) which can traverse across the membrane of virus-infected cells (transbodies) and could bind to-/interfere with- biological properties of the replicating virus proteins. Like transbodies to the influenza virus, hepatitis C virus, Ebola virus, and Dengue virus (206). Hence generating transbodies directed against CoV intracellular proteins such as papain-like proteases (PLpro), cysteine-like protease (3CLpro) or other non-structural proteins (nsp) that are pivotal for virus replication and transcription, could be a useful approach for safe, broadly effective passive immunization virus exposed subjects and as therapeutics for infected patients.

In a case study based on five grimly sick patients having symptoms of severe pneumonia due to COVID-19, convalescent plasma administration was found helpful in recovering these patients successfully. The convalescent plasma containing SARS-CoV-2 specific ELISA (serum) antibody titer higher than 1:1000 and neutralizing antibody titer more significant than 40 was collected from the recovered patients and used for plasma transfusion twice in the volume of 200-250 ml on the same day of collection (315). At present, treatment for sepsis and ARDS mainly involves antimicrobial therapy, source control, and supportive care. Hence the use of therapeutic plasma exchange can be considered as an option in managing such severe conditions. Further randomized trials can be designed to investigate its efficacy (316).

Potential therapeutic agents

Therapeutic options that could be evaluated and utilized for against SARS-CoV-2 infection comprise of molecules binding to the virus, molecules or inhibitors targetting specific enzymes implicated in viral replication and transcription, small-molecule inhibitors of the helicase, essential proteases or other proteins of the virus, host cell protease inhibitors and endocytosis inhibitors, siRNA, neutralizing antibodies, mAbs targeting host receptor, mAbs interfering with S1 RBD, anti-viral peptide targeting S2, and natural products (7, 166, 186). The S protein acts as the critical target for developing CoVs antiviral therapies such as

S protein inhibitors, S cleavage inhibitors, neutralizing antibodies, RBD–ACE2 blockers, siRNAs, fusion core blockers, and protease inhibitors (168).

All these therapeutic approaches have revealed both *in vitro* and *in vivo* anti-CoV potentials. Although *in vitro* researches were carried out with these therapeutics showing efficacy, however, mostly need appropriate support of randomized animal or human trials. Therefore they might be of limited applicability and require trials against SARS-CoV-2 to gain practical usefulness. The binding of SARS-CoV-2 with ACE2 leads to exacerbation of pneumonia as a consequence of the imbalance in the renin-angiotensin system (RAS). The virus-induced pulmonary inflammatory responses may be reduced by the administration of ACE-Inhibitors (ACEI) and angiotensin type-1 receptor (AT1R) (207).

Several investigations have suggested the use of small molecular inhibitors for the potential control of SARS-CoV infections. The drugs of the FDA-approved compound library were screened to identify four small molecular inhibitors of MERS-CoV (chlorpromazine, chloroquine, loperamide, and lopinavir) that inhibited the viral replication. These compounds also hinder the SARS CoV and human CoVs (208). Therapeutic strategies involving the use of specific antibodies or compounds that neutralize cytokines and their receptors will help to restrain the host inflammatory responses. Such drugs acting specifically in the respiratory tract will help to reduce virus-triggered immune-pathologies in COVID-19 (209). The later stages of coronavirus induced inflammatory cascade are characterized by the release of pro-inflammatory IL-1 family members such as IL-1 and IL-33. Hence, there exists a possibility that the inflammation associated with coronavirus can be inhibited by utilizing anti-inflammatory cytokines that belongs to the IL-1 family (92). It has also been suggested that the actin protein is the host factor that is involved in cell entry and pathogenesis of SARS-CoV-2. Hence, those drugs that modulate the biological activity of this protein, like ibuprofen, might have some therapeutic application in managing the disease (174). The plasma Angiotensin II level was found to be markedly elevated in COVID-19 infection and was correlated to viral load and lung injury. Hence, drugs that block angiotensin receptors may have the potential for treating COVID-19 infection (121). A scientist from Germany named Rolf Hilgenfeld has been working on the identification of drugs for the treatment of coronaviral infection from the time of SARS. He has now planned to visit Wuhan and test the drug molecules he has in animals. If they are found useful can be a cure to the current problem caused by the novel virus (19).

The SARS-CoV S2 subunit plays a significant role in mediating virus fusion that provides entry into the host cell. The heptad repeat 1 (HR1) and heptad repeat 2 (HR2) can interact and form a six-helical bundle that brings the viral and cellular membranes nearby, facilitating its fusion. The sequence alignment study conducted between COVID-19 and SARS-CoV identified that the S2 subunits are highly conserved in these CoVs. TheHR1 and HR2 domains showed 92.6% and 100% overall identity, respectively (210). From these findings, we can confirm the significance of COVID-19 HR1 and HR2 and its vital role in host cell entry. Hence, fusion inhibitors target the HR1 domain of S protein, thereby preventing viral fusion and entry into the host cell. It is another potential therapeutic strategy that can be used in the management of COVID-19. Other than the specific therapy directed against COVID-19, general treatments play a vital role in the enhancement of host immune response against the viral agent. Inadequate nutrition is associated with the weakening of the host immune response, making the individual more susceptible. The role played by nutrition

in disease susceptibility should be measured by evaluating the nutritional status of patients with COVID-19 (205).

Animal models and cell cultures

For studying the pathogenesis and evaluation of vaccines and therapeutics against CoVs, including SARS, MERS-CoVs, and the presently emerging SARS-CoV-2, suitable animal models that could mimic the clinical disease are needed (211,212). Various animal models have been assessed for SARS- and MERS-CoVs such as a mouse, guinea pigs, golden Syrian hamsters, ferrets, rabbits, non-human primates like rhesus macaques and marmosets, and cats (185, 213-218). The specificity of the virus to human ACE2 (hACE2; receptor of SARS-CoV) was found to be a significant hindrance in developing animal models for SARS-CoV. Consequently, a SARS-CoV transgenic mouse model was developed by inserting the hACE2 gene into the mouse genome (219). The inability of MERS-CoV to replicate in the respiratory tracts of animals (mice, hamsters, and ferrets) is another limiting factor. However, with genetic engineering, 288-330+/+ MERS-CoV genetically modified mouse model was developed and now is in use for the evaluation of novel drugs and vaccines against MERS-CoV (220). In the past, the small animals (mice or hamsters) have been targeted for closer to humanized structure, such as mice altered DPP4 with hDPP4human, hDPP4-transduced mice, and hDPP4-Tg mice (transgenic for expressing hDPP4) for MERS-CoV infection (221). CRISPR-Cas9 gene-editing tool has been used for inserting the genomic alterations in mouse, making them susceptible to MERS-CoV infection (222). Efforts are on the way to recognize suitable animal models for SARS-CoV2 /COVID-19, identify the receptor affinity of this virus, studying pathology in experimental animal models, exploring virus-specific immune responses and protection studies, which together would give a pace to efforts being made for developing effective vaccines and drugs against this emerging virus. Cell lines such as monkey epithelial cell lines (LLC-MK2 and Vero-B4), goat lung cells, alpaca kidney cells, dromedary umbilical cord cells, advanced *ex vivo* three-dimensional (3D) tracheobronchial tissue have been explored to study human CoVs (MERS-CoV)(223, 224). Vero and the Huh-7 cells (human liver cancer cells) have been used for isolating the SARS-CoV-2 (194).

Recently, in an animal model using rhesus monkeys, authors found that neither viral loads in nasopharyngeal and anal swabs along the timeline nor viral replication in all primary tissue compartments at five days post-reinfection was found in re-exposed monkeys (279). Combined with the follow-up virologic, radiological, and pathological findings, the monkeys with re-exposure showed no recurrence of COVID-19, similarly to the infected monkey without rechallenge. Taken together, their results indicated that the primary SARS-CoV-2 infection could protect from subsequent exposures, which have the reference of prognosis of the disease and vital implications for vaccine design (279).

PREVENTION, CONTROL, AND MANAGEMENT

In contrast to China's response to the 2002 SARS outbreak, they have shown immense political openness in reporting the COVID-19 outbreak promptly. They have also performed rapid sequencing of COVID-19 at multiple levels and shared the findings globally within days of identifying the novel virus (225). The move made by China opened a new chapter in global health security and diplomacy. Even though complete lockdown was

declared following the COVID-19 outbreak in Wuhan, large-scale movement of people has resulted in a radiating spread of infections in the surrounding provinces as well as to several other countries. Large-scale screening programs might help us to control the spread of this virus. However, this is both challenging as well as time-consuming due to the present extent of infection (226). The current scenario warrants the need for implementing robust preventive and control measures due to the potential of COVID-19 for nosocomial infections (68). A follow-up of infected patients by telephone on day seven and day 14 are advised to avoid any further unintentional spread or nosocomial transmission (317). The availability of public datasets provided by independent analytical teams will act as robust evidence that would guide us in designing interventions against the COVID-19 outbreak. The newspaper reports and social media can be used to analyze and reconstruct the progression of an outbreak. They can help us to obtain detailed patient-level data in the early stages of an outbreak (227). The immediate travel restrictions imposed by several countries might have contributed significantly to prevent the spread of SARS-CoV-2 globally (89, 228). Following the outbreak, a temporary ban was imposed on the wildlife trade, keeping in mind the possible role played by wild animal species in the origin of SARS-CoV-2/COVID-19 (147). Taking a permanent and bold decision on the trade of wild animal species is necessary to prevent the possibility of the virus spread and initiation of an outbreak due to zoonotic spillover (1).

Personal protective equipments (PPE) like face masks will help to prevent the spread of respiratory infections like COVID-19. Face masks not only protect from infectious aerosols but also prevent the transmission of disease to other susceptible individuals while traveling through public transport systems (318). Another critical practice that can reduce the transmission of respiratory diseases is the maintenance of hand hygiene. However, the efficacy of this practice in reducing transmission of respiratory viruses like SARS-CoV-2 is much dependent upon the size of droplets produced. Hand hygiene will reduce disease transmission only if the virus transmitted through the formation of large droplets (319). Hence, it is better not to overemphasize that hand hygiene will prevent transmission of SARS-CoV-2 since it may produce a false sense of safety among the general public that further contribute to the transmission of COVID-19. Even though airborne spread has not been reported in SARS-CoV-2 infection, transmission can occur through droplets and fomites, especially when there is close unprotected contact between the infected and susceptible individuals. Hence, hand hygiene is equally important as the use of appropriate PPE like face masks to break the transmission cycle of the virus—both hand hygiene and face masking help to reduce the risk of COVID-19 transmission (320).

Medical staffs come under the riskiest group of individuals that can get the COVID-19 infection. This is because they are exposed directly to the frontline of infected patients. Hence, proper training must be given to all the hospital staff on methods of prevention and protection so that they become competent enough to protect themselves and others from this deadly disease (321). As a preventive measure, healthcare workers caring for infected patients should take extreme precautions against both contact and airborne transmission. They should use PPE such as face masks (N95 or FFP3), eye protection (goggles), gowns, and gloves to nullify the risk of infection (304).

The human-to-human transmission reported in SARS-CoV-2 infection occurs mainly through droplet or direct contact. Due to this, the first-line healthcare workers should follow stringent infection control and preventive measures such as the use of PPE to prevent the risk

of infection (110). The mental health of the medical/health workers who are involved in the COVID-19 outbreak is of great importance because this will affect their attention, concentration, and decision-making capacity. Hence, for control of the COVID-19 outbreak, rapid steps are to be taken to protect the mental health of medical workers (229) since the living mammals sold in the wet market are suspected to be the intermediate host of SARS-CoV-2. There is a need for strengthening the regulatory mechanism for wild animal trade (13). The total number of COVID-19 confirmed cases is on a continuous rise, and the cure rate is relatively low, making the disease control very difficult to achieve. The Chinese government is making continuous efforts to contain the disease by taking emergency control and prevention measures. They have already built a hospital for patients affected by this virus and are currently building several more for accommodating the continuously increasing infected population (230). The effective control of SARS-CoV-2/COVID-19 requires high-level interventions like intensive contact tracing, as well as quarantine of suspected and isolation of infected individuals. Implementation of rigorous control and preventive measures, all together, might control the reproduction number and reduce the transmission risk (228). Considering the zoonotic links associated with SARS-CoV-2, the one health approach may play a vital role in the prevention and control measures being followed to restrain this pandemic virus (322-324). The substantial importation of COVID-19 pre-symptomatic cases from Wuhan has resulted in independent, self-sustaining outbreaks across the major cities both within the country and across the globe. The majority of the Chinese cities are now facing localized outbreaks of COVID-19 (231). Hence, deploying efficient public health interventions might help to cut the spread of this virus globally.

The occurrence of COVID-19 infection in two cruise ships gave us the preliminary idea regarding the transmission pattern of the disease. Cruise ships act as a close environment and provide an ideal setting for the occurrence of respiratory disease outbreaks. Such an environment poses a significant threat to travelers since people from different countries are on board that favors the introduction of the pathogen (325). The two major cruise ship that got involved in the COVID-19 outbreaks were the Diamond Princess and Grand Princess. The number of confirmed COVID-19 cases around the world are on the rise. The success of preventive measures put forward by every country is mainly dependent upon their ability to anticipate the oncoming waves of patients. This will help to properly prepare the healthcare workers and increase the intensive care unit (ICU) capacity (326). Instead of entirely relying on lockdown protocols, countries should focus mainly on the alternative intervention strategies such as large-scale testing, contract tracing, and localized quarantine of suspected cases for limiting the spread of this pandemic virus. Such intervention strategies will be useful either at the beginning of the pandemic or after lockdown relaxation (327). Lockdown should be imposed only to slow down the disease progression among the population so that the health-care system is not overloaded.

The reproduction number (R_0) of COVID-19 infection was earlier estimated to be in the range of 1.4-2.5 (70), and recently, it is estimated to be 2.24 to 3.58 (76). When compared to their coronavirus predecessors, COVID-19 has anR_0 value that is greater than that of MERS (R_0 <1) (108) but less than that of SARS (R_0 value of2-5) (93). Still, to prevent further spread of disease mass gatherings, functions remain canceled in the affected cities, and persons are also asked to work from home (232). Hence, it is a relief that the current outbreak of COVID-19 infection can be brought under control with the adoption of strategic preventive and control measures along with the early isolation of subsequent cases in the

coming days. Studies also report that since the air traffic between China and African countries increased many folds in the past decade after the SARS outbreak, African countries need to be vigilant to prevent the spread of novel coronavirus in Africa (225). Due to fear of virus spread, Wuhan city has been completely shut down (233). The immediate control over the ongoing COVID-19 outbreaks appears a mammoth task, especially for the third world and developing countries due to their inability to allocate quarantine stations that could screen infected individuals' movement (234). Such underdeveloped countries should divert their resources and energy on enforcing the primary level of preventive measures like controlling the entry of individuals from China or countries where the disease has flared-up, isolating the infected individuals, and quarantine of suspected individuals. Most of the sub-Saharan African countries have a fragile health system that gets crippled in the event of an outbreak. Effective management of COVID-19 would be difficult for low-income countries due to their inability to respond rapidly due to the lack of an efficient health care system (65). Controlling the imported cases is critical in preventing the spread of COVID-19 to other countries that have not reported the disease until now. The probability that an imported case of COVID-19 is followed by sustained human-to-human transmission was estimated to be 0.41. This can be reduced to a value of 0.012 by decreasing the meantime from the onset of symptoms to hospitalization by half and can only be made possible by using intense disease surveillance systems (235). The silent importations of infected individuals (before the manifestation of clinical signs) also contributed significantly to the spread of disease across the major cities of the world. Even though the travel ban was hosted in Wuhan (89), infected persons who traveled out of the city just before the imposition of the ban might have remained undetected and resulted in local outbreaks (236). Emerging novel diseases like COVID-19 are challenging to be contained within the country of origin since globalization has led to a world without borders. Hence, international collaboration plays a vital role in preventing the further spread of this virus across the globe (237).

We also predict the possibility of another outbreak, as predicted by Fan et al. (6). The present outbreak caused by SARS-CoV-2 (COVID-19) was indeed expected. Similar to previous outbreaks, the current outbreak will also be contained shortly. However, the real question is, how are we planning to counter the next zoonotic CoV epidemic that is likely to occur within the next 5–10 years or perhaps within a lesser time? (**Fig. 7**).

CONCLUDING REMARKS

Several years after the global SARS epidemic, the current SARS-CoV-2/COVID-19 pandemic has served as a reminder of how novel pathogens can rapidly emerge and spread through the human population, which may eventually cause severe public health crises. Further research should be conducted to establish animal models for SARS-CoV-2to investigate replication, transmission dynamics, and pathogenesis in humans. This may help develop and evaluate potential therapeutic strategies against zoonotic CoV epidemics. Present trends suggest the occurrence of future outbreaks of CoVs due to changes in climate, and ecological conditions may be associated with human-animal contact. Live-animal markets, such as the Huanan South China Seafood Market, represent ideal conditions for inter-species contact of wildlife with domestic birds, pigs, and mammals, which substantially increases the

probability of inter-species transmission of CoV infections and could result in high risks to humans due to adaptive genetic recombination in these viruses (328-330).

The COVID-19 associated symptoms such as fever, cough, expectoration, headache, and myalgia or fatigue. Individuals with asymptomatic and atypical clinical manifestations were also identified recently, further adding to the complexity of disease transmission dynamics. Atypical clinical manifestations may only express symptoms such as fatigue instead of the respiratory signs such as fever, cough, and sputum. In such cases, the clinician must be vigilant for the possible occurrence of asymptomatic and atypical clinical manifestations to avoid the possibility of missed diagnosis.

The present outbreak caused by SARS-CoV-2 was indeed expected. Similar to previous outbreaks, the current outbreak will also be contained shortly. However, the real question is, how are we planning to counter the next zoonotic CoV epidemic that is likely to occur within the next 5–10 years or perhaps within a lesser time? Our knowledge of most of the bat CoVs is scarce as these viruses have not been isolated and studied, and extensive studies on such viruses are typically only conducted when they are associated with specific disease outbreaks. The next step following the control of the COVID-19 outbreak in China should be focused on screening, identification, isolation, and characterization of CoVs present in wildlife species of China, particularly in bats. Both *in vitro* and *in vivo* studies (using suitable animal models) should be conducted to evaluate the risk of future epidemics. Presently, licensed antiviral drugs or vaccines against SARS-CoV, MERS-CoV, and SARS-CoV-2 are lacking. However, advances in designing antiviral drugs and vaccines against several other emerging diseases will help develop suitable therapeutic agents against COVID-19 in a short time. Until then, we must rely exclusively on various control and prevention measures to prevent this new disease from becoming a pandemic.

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Yashpal Singh Malik, M.V.Sc., Ph.D., serving as ICAR-National Fellow and Professor is an expert on enteric viral infections, zoonosis, and emerging viral diseases of animals and humans. He contributed immensely to viral disease epidemiology, virus-host interactions, microbial biodiversity, characterization, and diagnosis of pathogens. He did Postdoc from the University of Minnesota, USA. He acquired advanced training in molecular virology from the Division of Virology, University of Ottawa, Canada, and Wuhan Institute of Virology, China. He has represented India in the scientific arena in more than 12 countries. He is the Secretary-General of Indian Virological Society and Secretary-E for the World Society for Virology (USA). He is a study group member of ICTV

on *Birnaviridae* and *Picobirnaviridae*. He has authored five books of reputed publishers, including Elsevier and Springer Nature, and has published 225 scientific research articles, reviews in journals of high impact factor. His h-index is 28, and the RG score is 38.6.

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Wanpen Chaicumpa, D.V.M. (Hons.), Ph.D. (Microbiology), is Emeritus Professor, Research Consultant and Head of the Center of Research Excellence on Therapeutic Proteins and Antibody Engineering, at Department of Parasitology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, and consultant of the Faculty of Allied Health Sciences, Thammasat University, Thailand. Her research interests are intestinal immunity against enteric infections, vaccine development, immuno- and molecular diagnoses of tropical infections; allergy; immunotherapy, and antibody engineering. She is an executive member of the Thailand Academy of Sciences. She has served as Editor in Chief of Asian Pacific J Allergy & Immunology. She served as a consultant to the WHO Southeast Asian Regional Office, India. She published over 250 publications and owned more than 30 patents/patent applications; three textbooks (Animal viruses, Immunology for Diagnosis of Diseases, and Practical Immunology for Students of Diploma of Tropical Medicines).

D. Katterine Bonilla-Aldana, D.V.M., M.Sc., graduated from Universidad de la Amazonia, School of Veterinary Medicine and Zootechnics, in Florencia, Colombia, 2015. She completed a Master of Sciences in Microbiology, Universidad Metropolitana, Barranquilla, Colombia, in 2019. She served as Young Researcher, Public Health and Infection Research Group, Faculty of Health Sciences, Universidad Tecnológica de Pereira (UTP) in Pereira, Risaralda, Colombia. She is a member of the Colombian Infectious Diseases Association (ACIN) and the International Society for Infectious Diseases. She is a member of the Committee on Tropical Medicine, Zoonoses, and Travel Medicine of ACIN. She has been recognized as Junior Researcher, Ministry of Science in Colombia, MinCiencias. She is a Professor of Veterinary Medicine and Zootechnics, Fundación Universitaria Autónoma de las Americas (FUAM), in Pereira, Risaralda, Colombia. She is a

Leader Professor of the Zoonoses Research Incubator (SIZOO), FUAM. Her main research interest is the study of zoonotic tick-borne and vector-borne diseases.

Alfonso J. Rodriguez-Morales, M.D., M.Sc., D.T.M.&H., F.R.S.T.M.H.(Lon), F.F.T.M. R.C.P.S.(Glasg), F.A.C.E., Ph.D.(c), Hon.D.Sc., is an Expert in Tropical and Emerging Diseases, particularly in Zoonotic and Vector-Borne Diseases. He is President of the Travel Medicine Committee, Pan American Infectious Diseases Association (API), as well as the Vicepresident, Colombian Infectious Diseases Association (ACIN). He is a member of the Committee on Tropical Medicine, Zoonoses, and Travel Medicine, ACIN. He is part of the Executive Board of the Latin American Society for Travel Medicine (SLAMVI) and of the Council of the International Society for Infectious Diseases. Since 2014, he has been recognized as Senior Researcher, Ministry of Science in Colombia, MinCiencias. He is a Professor of the Faculty of Health Sciences of the Universidad Tecnológica de Pereira (UTP) in Pereira, Risaralda, Colombia. He is Co-Director of the Public Health and Infection Research Group, UTP, classified A1 by Colciencias. His Scopus H index is currently 30 (Google-Scholar H index 45).

Table 1. FDA-approved In Vitro Emergency Authorization Use Diagnostics Available for SARS-CoV-2, as of March 30, 2020 (260, 261).

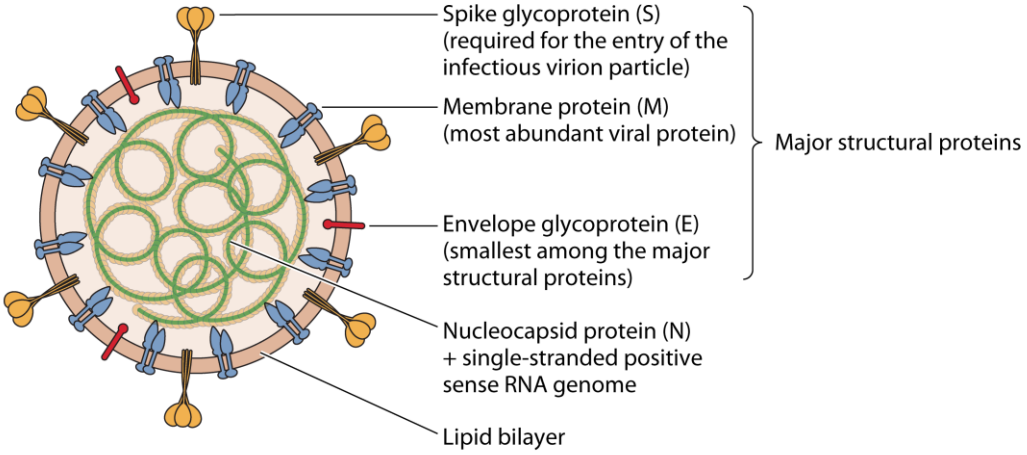
Developer	**Diagnostic Platform**
Centers for Disease Control and Prevention's (CDC)	CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel (CDC)
Wadsworth Center, New York State Department of Public Health's (CDC)	New York SARS-CoV-2 Real-time Reverse Transcriptase (RT)-PCR Diagnostic Panel
Roche Molecular Systems, Inc. (RMS)	cobas SARS-CoV-2
Thermo Fisher Scientific, Inc.	TaqPath COVID-19 Combo Kit
Laboratory Corporation of America (LabCorp)	COVID-19 RT-PCR Test
Hologic, Inc.	Panther Fusion SARS-CoV-2
Quest Diagnostics Infectious Disease, Inc.	Quest SARS-CoV-2 rRT-PCR
Quidel Corporation	Lyra SARS-CoV-2 Assay
Abbott Molecular	Abbott RealTime SARS-CoV-2 assay
GenMark Diagnostics, Inc.	ePlex SARS-CoV-2 Test
DiaSorin Molecular LLC	Simplexa COVID-19 Direct assay
Cepheid	Xpert Xpress SARS-CoV-2 test
Primerdesign Ltd.	Primerdesign Ltd COVID-19 genesig Real-Time PCR assay
Mesa Biotech Inc.	Accula SARS-Cov-2 Test
BioFire Defense, LLC	BioFire COVID-19 Test
PerkinElmer, Inc.	PerkinElmer New Coronavirus Nucleic Acid Detection Kit
Avellino Lab USA, Inc.	AvellinoCoV2 test
BGI Genomics Co. Ltd	Real-Time Fluorescent RT-PCR Kit for Detecting SARS-2019-nCoV
Luminex Molecular Diagnostics, Inc.	NxTAG CoV Extended Panel Assay
Abbott Diagnostics Scarborough, Inc.	ID NOW COVID-19
QIAGEN GmbH	QIAstat-Dx Respiratory SARS-CoV-2 Panel
NeuMoDx Molecular, Inc.	NeuMoDx SARS-CoV-2 Assay

Table 2. Clinical specimens for detection of SARS CoV-2

Sample	**Recommendation***
Bronchoalveolar lavage fluid	+++
Sputum	+++
Nasal swabs	+++
Fibrobronchoscope brush biopsy	++
Pharyngeal swabs	++
Feces	+
Blood	+
Urine	+

*Based on (245, 246). +++, strong; ++, moderate; +, weak.

FIG1: SARS-CoV-2 virus structure



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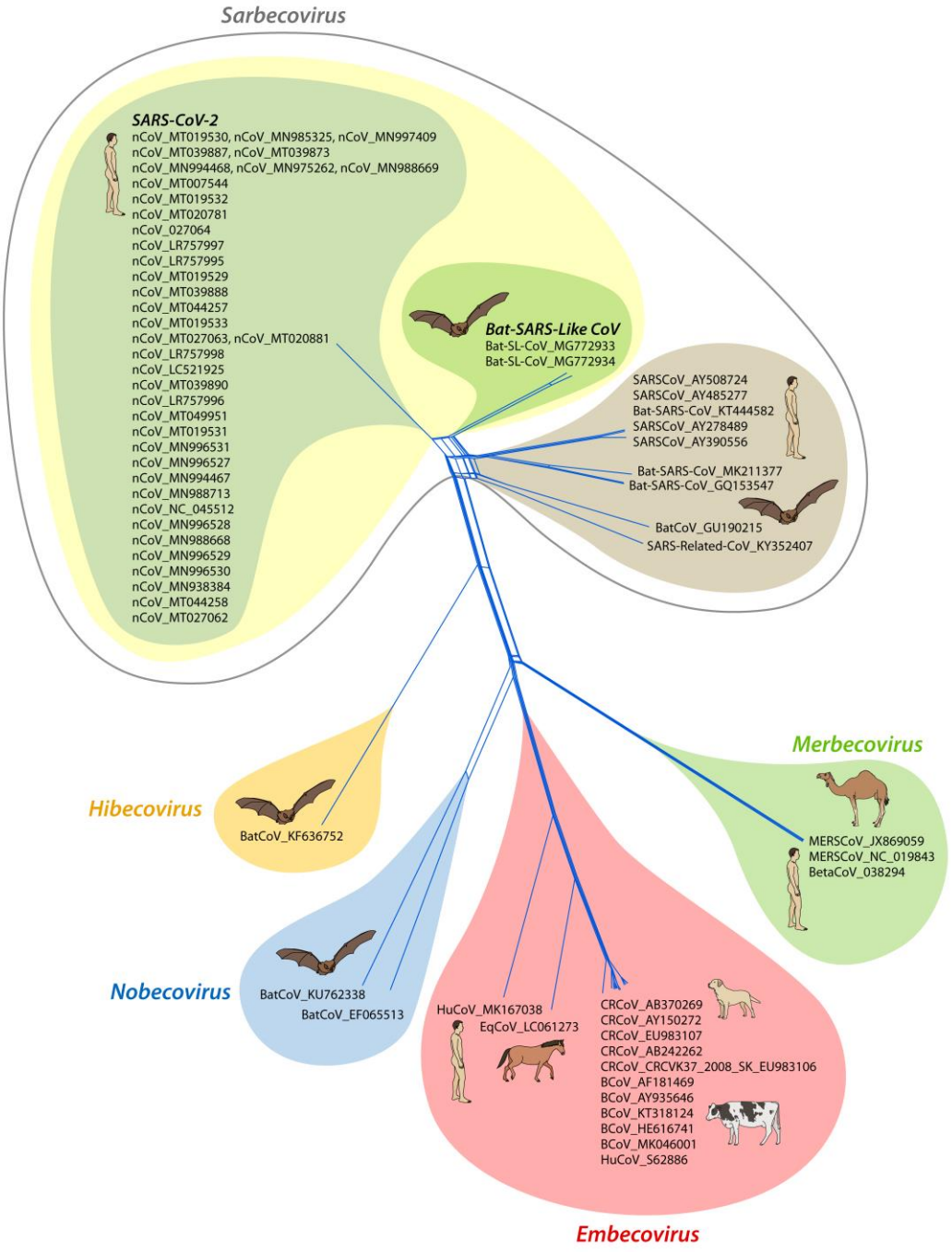
Peer-reviewed version available at Clinical Microbiology Reviews 2020, 33; doi:10.1128/CMR.00028-20

FIG 2: S-Gene Splits Tree Analysis: Spike (S) glycoprotein gene-based phylogenetic analysis (Splits-Tree 4.0) of SAR-CoV-2 isolates (39 isolates). The SARS-CoV-2 isolates analyzed with related CoVs from past human outbreaks and of animal-origin, including MERS-CoV, bovine coronavirus, canine coronavirus, bat_coronaviruses, Bat-SL-SARS-CoV and equine CoV. The analysis includes all the defined five subgenera of *Betacoronaviruses*, namely *Sarbecovirus*, *Embecovirus*, *Merbecovirus*, *Nobecovirus*, and*Hibecovirus*. The grey area covered isolates are from the current outbreak of SARS-CoV-2 from the world over. The nearest neighbors of SARS-CoV-2 are the Bat-SL-CoV, encircled in yellow color.



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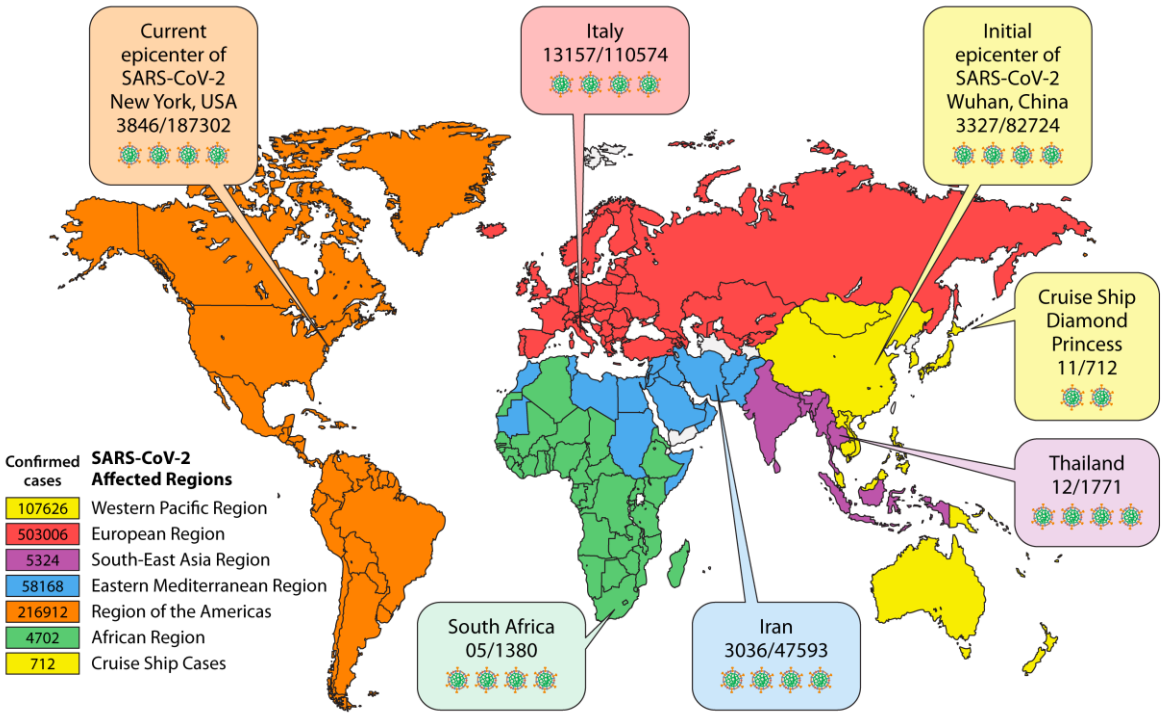
Peer-reviewed version available at *Clinical Microbiology Reviews* **2020**, *33*; doi:10.1128/CMR.00028-20

FIG 3: World Map depicting the current scenario of COVID-19. Countries, territories or regions with reported confirmed cases of SARS-CoV-2 as of April 3, 2020. Different colors indicate different geographical regions with the number of confirmed cases. The region-wise total number of confirmed cases is depicted in different color strips—meaningful information on confirmed cases and deaths from different countries or regions depicted in circled balloons.

Source: WHO https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200402-sitrep-73-covid-19.pdf?sfvrsn=5ae25bc7_2

Updated number of cases, deaths, and patients recovered can be found at https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6.



Region wise number of confirmed cases based on 73rd situation report of WHO, accessed on 03rd April, 2020

FIG 4: Bar graph and Pie chart for cases and deaths: Laboratory confirmed cases and deaths in China and the world over due to SARS-CoV-2. A1) SARS-CoV-2 confirmed cases outside China where more than 100 deaths have been reported to WHO till April 2, 2020. **A2)** Total deaths and cases in China only. **A3)** Number of total deaths worldwide outside China.

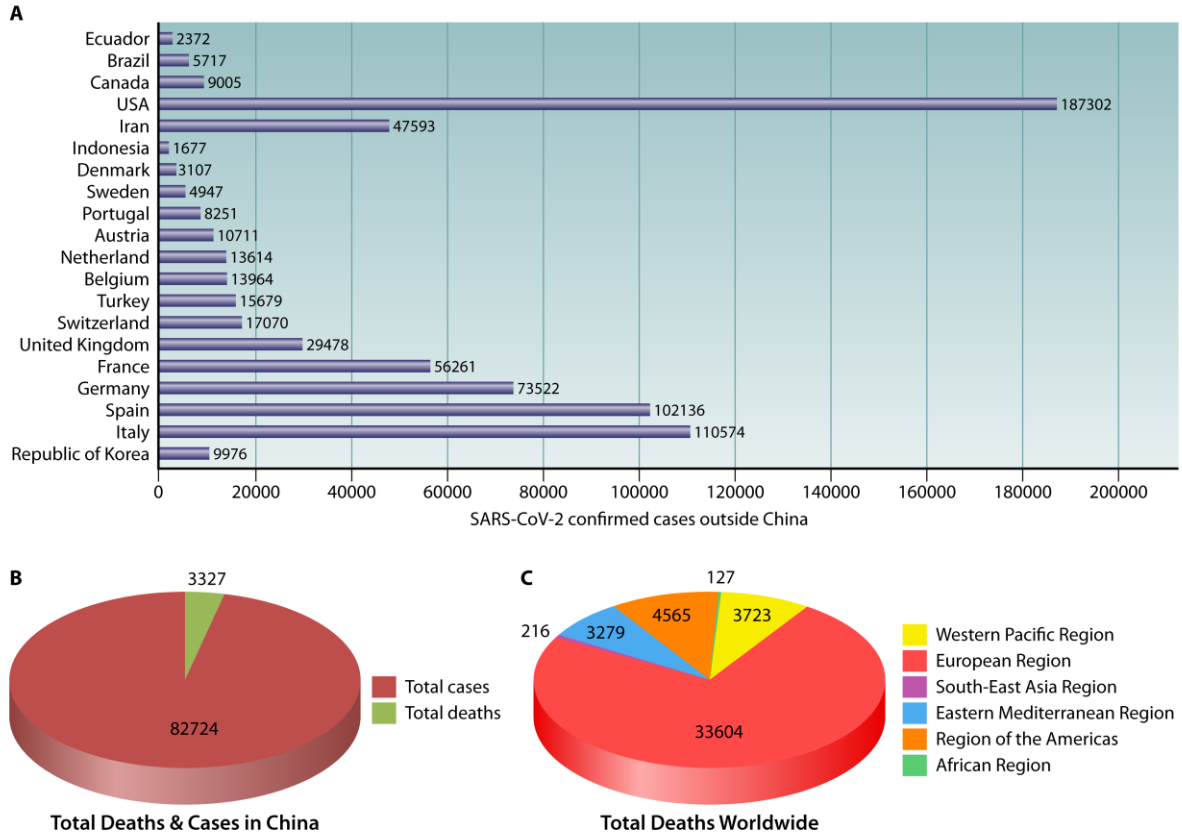


FIG 5: Timeline depicting the significant events that occurred during the SARS-CoV-2/COVID-19 virus outbreak. The timeline describes the significant events during the current SARS-CoV-2 outbreak starting from December 8, 2019, and has been shown till April 2, 2020.

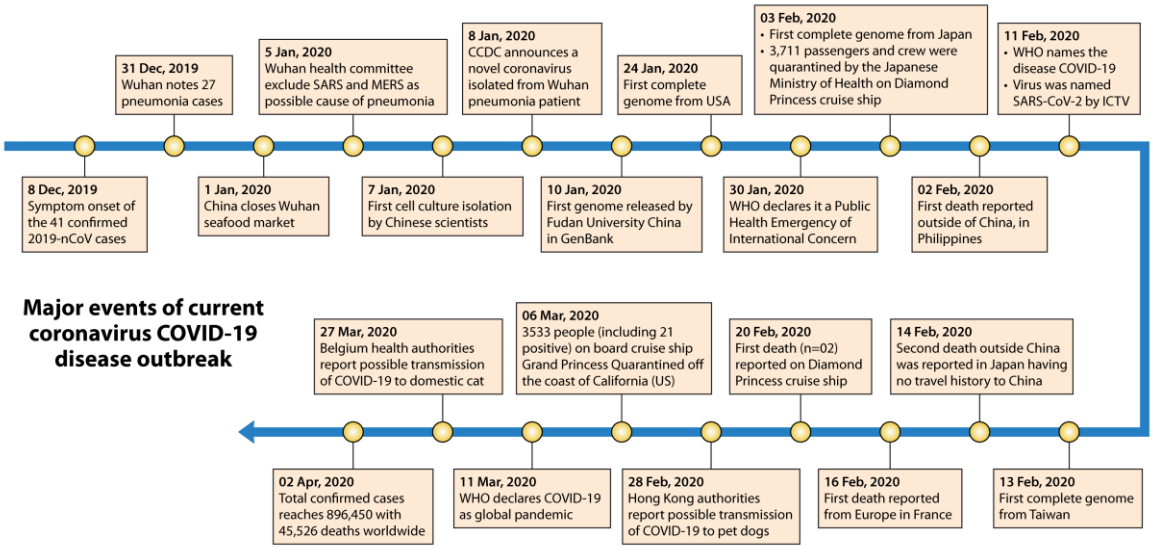


FIG 6: Potential transmission routes for SARS-CoV-2

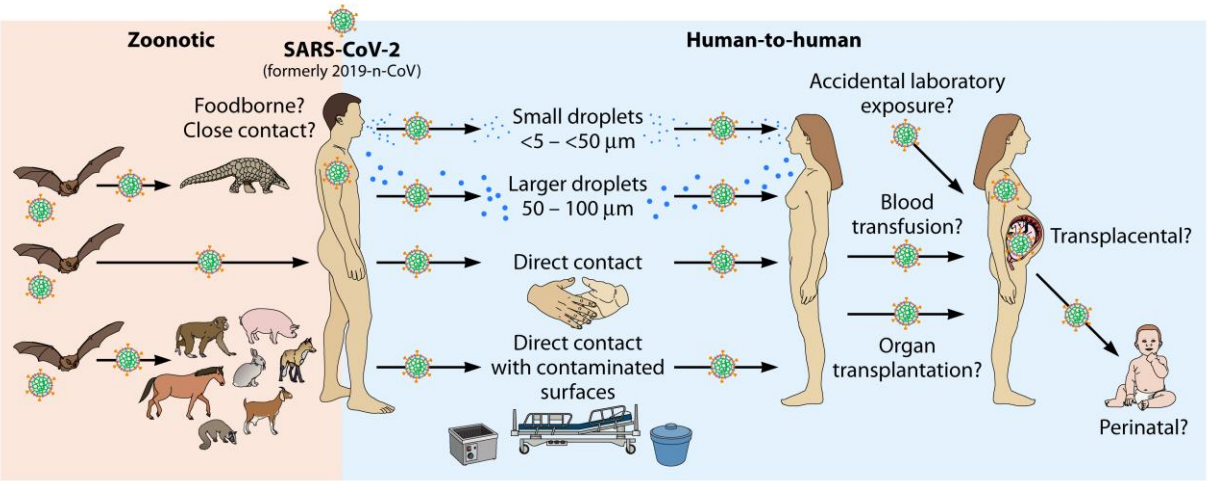


FIG 7: Coronaviruses origins. Coronavirus is the most prominent example of an emerging virus that has crossed the species barrier from wild animals to humans, like SARS and MERS. The origin of SARS-CoV-2 is also suspected to be from an intermediate animal host. The possibility of crossing the species barrier again for the fourth time cannot be ruled out.