Coronavirus Disease 2019 – COVID-19

Kuldeep Dhama,[a] Khan Sharun,[b] Ruchi Tiwari,[c] Shubhankar Sircar,[d] Sudipta Bhat,[d] Yashpal Singh Malik,[d*], Karam Pal Singh,[a] Wanpen Chaicumpa,[e] D. Katterine Bonilla-Aldana,[f,g], Alfonso J Rodriguez-Morales.[g,h*]

Affiliations:

[a]Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly- 243 122, Uttar Pradesh, India.

[b]Division of Surgery, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly- 243 122, Uttar Pradesh, India.

[c]Department of Veterinary Microbiology and Immunology, College of Veterinary Sciences, Uttar Pradesh Pandit Deen Dayal Upadhyaya Pashu Chikitsa Vigyan Vishwavidyalaya Evam Go Anusandhan Sansthan (DUVASU), Mathura, India –281001, India.

[d]Division of Biological Standardization, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly- 243 122, Uttar Pradesh, India.

[e]Center of Research Excellence on Therapeutic Proteins and Antibody Engineering, Department of Parasitology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

[f]Semillero de Zoonosis, Grupo de Investigación BIOECOS, Fundación Universitaria Autónoma de las Américas, Sede Pereira, Pereira, Risaralda, Colombia.

[g]Public Health and Infection Research Group, Faculty of Health Sciences, Universidad Tecnologica de Pereira, Pereira, Colombia.

[h]Grupo de Investigacion Biomedicina, Faculty of Medicine, FundacionUniversitariaAutonoma de las Americas, Pereira, Risaralda, Colombia.

Corresponding Author(s):

Yashpal Singh Malik, PhD (malikyps@gmail.com), Division of Biological Standardization, ICAR – Indian Veterinary Research Institute, Izatnagar 243122, Bareilly, Uttar Pradesh, India.

Alfonso J Rodriguez-Morales, HonDSc (arodriguezm@utp.edu.co), Public Health and Infection Research Group, Faculty of Health Sciences, Universidad Tecnologica de Pereira, Pereira, Colombia; Grupo de Investigacion Biomedicina, Faculty of Medicine, FundacionUniversitariaAutonoma de las Americas, Pereira, Risaralda, Colombia.

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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 (CoV). 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 CoV 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 a less severe pathogenesis but higher transmission competence, as is evident from the continuously increasing number of confirmed cases. 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 CoV has emerged in 2019/2020 which may pose a global health threat given the ongoing epidemic in China and other 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". 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 (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 coronaviruses were known to infect humans include 229E, NL63, OC43, 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. 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 currentlymaking 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 re-combination (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, while less

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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-19 has been found to be 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 in*in vitro* studies; however, these treatments have to datenot undergone any randomized animal or human clinical trials, which limit their practical applicability in the current epidemic (7, 9, 19-21).

The present comprehensive review describes the various features of 2019-Novel Coronavirus [SARS-CoV-2 (2019-nCoV)] causing the current disease outbreaks (COVID-19), 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 (22) and to provide a feasible one health strategy for the management of this fatal virus.

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). The recently emerging 2019-Novel Coronavirus [SARS-CoV-2 (2019-nCoV)] has caused havoc in China and threats 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 World Health Organization (WHO) announced an official name for this disease as COVID-19. For the time being, earlier the WHO named this currently emerging virus as 2019-new/novel coronavirus (2019-nCoV) (25). Most recently, this virus has been proposed to be designated/named as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) by the International Committee on

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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 as a sister to SARS-CoVs (26). The 2019-nCoV 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).

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 2019-nCoV is of 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 2019-nCoV 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 2019-nCoVhas also been found to be arranged similarly and encodes several accessory proteins, although 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 2019-nCoV is considered as a new *Betacoronavirus* belonging to the subgenus *Sarbecovirus* (3). Few other important zoonotic viruses (MERS-related-CoV and SARS-related-CoV) also belong to the same genus, however the 2019-nCoV was identified as as distinct virus based on the percent identity with other *Betacoronavirus*, conserved ORF 1ab has beenf ound to be below than 90% (3). An overall 80% nuceleotide identity was observed between 2019-nCoV and original SARS-CoV along with 89% identity with ZC45 and ZXC21 SARS related coronaviruses of bats (2, 31, 36). In addition to this, 82% identity has been observed between 2019-nCoV 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 2019-nCoV (37). Phylogenetic analysis of the structural genes also made known that 2019-nCoV is closer to bat SARS-related-CoV. Therefore, SARS-CoV-2 might have originated from bats, while other amplifier hosts migh thave played possible rolefor 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). But 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 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

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individual nsps [Main protease (Mpro), chymotrypsin-like protease (3CLpro), and papain-like protease (PLPs)] (42). The 2019-nCoV also encodes these nsps, and their functions have been elucitaed recently (31). Remarkably, a difference between 2019-nCoV and other CoVsis the identification of a novel short putative protein within ORF3b, and 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 coronaviruses capable of inducing host immune response (45). The ectodomain in all coronaviruses 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, is responsible 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 virus with 9 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 observed in a familial cluster indicating that the viral evolution might have occurred during person-to-person transmission (4, 47). Such adaptive evolutions are common 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

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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 (2019-nCoV) does not have any 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 anexcellent C terminal domain (51). The SARS-CoV-2 (2019-nCoV) 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 withviral 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, possibly through 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 host by working as an antagonist for interferon and RNA interference (62). In comparison to SARS-CoV, the N protein of 2019-nCoVpossess 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-2 genome contains 15 nsps, nsp1-nsp10 and nsp12-16 and 8 accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, and orf14) (16). All these proteins play a specific role in viral replication (27). The difference in respect to the accessory proteins with SARS-CoV, SARS-CoV-2 (2019-nCoV) 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).

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The virus structure of 2019-nCoV is depicted in **Fig. 1.**

SARS-CoV-2 spike glycoprotein gene analysis

i. Sequence per cent similarity analysis

We assessed the nucleotide (NT) percent similarity using 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 highest similarity with Bat-SL-CoV with the NT per cent 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 per cent similarity was 55.4%, 45.5% to 47.9%, 46.2% to 46.6% and 45.0% to 46.3% with other four subgenera namely *Hibecovirus, Nobecovirus*, *Merbecovirus,* and *Embecovirus*, respectively. The per cent similarity index of current outbreak isolates signposts a close relationship of SARS-CoV-2 isolates to Bat-SL-CoV indicating a common origin. However, concrete evidences 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 belongs to the subgenus of *Sarbecovirus* falling inside the diverse range of *Betacoronaviruses.* There possible ancestor was hypothesized to be of bat CoV strains wherein bats might have played the crucial part in harbouring this class of viruses.

ii. Splits-Tree phylogeny analysis

In the unrooted phylogenetic tree of different betacoronaviruses based on the spike 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 closely in the splits-tree and divided in three sub clusters namely SARS-CoV-2, Bat-SARS-like-CoV (Bat-SL-CoV) and SARS-CoVs (**Fig. 2**). In 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 comes under the subgenus *Sarbecovirus* of *Orthocoronavirinae* subfamily and is entirely different from the viruses responsible for Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) (3). The newly emerged SARS-CoV-2 (2019-nCoV) 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 February 22, 2020, a total number of 77,794 cases of COVID-19 (with 2,359 deaths) have been reported from 29 countries worldwide (WHO situation report, 25 **Fig. 3**). The epicentre of the current SARS-CoV-2 (China) reported maximum deaths associated with COVID-19 (76,392 laboratory confirmed cases with 2,348 deaths; **Fig. 4**). The SARS-

CoV-2 confirmed cases have been reported from 28 countries apart from China. The affected countries include Republic of Korea (346), Japan (105), Singapore (86), United States of America (35), Thailand (35), Malaysia (22), Australia (21), Iran (18), Viet Nam (16), Germany (16), France (12), United Arab Emirates (11), Italy (9), The United Kingdom (9), Canada (8), Philippines (3), India (3), Russian Federation (2), Spain (2), Cambodia (1), Nepal (1), Sri Lanka (1), Belgium (1), Finland (1), Israel (1), Sweden (1), Egypt (1), Lebanon (1) **(Fig. 3, Fig. 4).** (25, 64). 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).

Besides China, deaths associated with SARS-CoV-2/COVID-19 infection have also been reported in Republic of Korea (2), Philippines (1), Japan (1), France (1) and Iran (4) (**Fig. 4**). The COVID-19 has also been confirmed on a cruise ship named 'Diamond Princes' quarantined in the Japanese water territory (Port of Yokohama). The ship is now the hot-bed for the COVID-2019 infections outside China with 634 cases and 2 deaths (**Fig. 3, Fig. 4)**. The major events occurred during SARS-CoV-2/COVID-19 virus outbreak from 8th Dec. 2019 and till 20 Feb 2020 are presented as a timeline depiction in **Fig. 5.**

In the current scenario, China is bearing the majority of the burden associated with COVID-19 in the form of disease morbidity and mortality compared to other countries (65). The COVID-19 outbreak was also associated with severe economic impact globally due to thesudden 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 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 fastwhen 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 2019-nCoVto 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 (2019-nCoV) 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

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403 further investigations, since it is a latent possibility (1). Additionally, to that, other potential
404 and expected routes would be associated with transmission, as in other respiratory viruses, by
405 direct contact, shaking contaminated hands, or by direct contact with contaminated surfaces
406 (**Fig. 6**). Still to be better defined, yet need to be answer if blood transfusion and organ
407 transplantation, as well as transplacental and perinatal routes would be possible for SARS-
408 CoV-2 transmission (**Fig.6**).

409 From experience with several outbreaks associated with known emerging viruses,
410 higher pathogenicity of the virus is often associated with lower transmissibility. Compared to
411 the emerging viruses like Ebola virus, Avian H7N9, SARS-CoV, and MERS-CoV, the
412 SARS-CoV-2 (2019-nCoV) have relatively lower pathogenicity and moderate
413 transmissibility (15). The risk of death among the individuals infected with COVID-19 was
414 calculated using infection fatality risk (IFR). The IFR was found to be in the range of 0.3% to
415 0.6% that is comparable to previously occurred Asian influenza pandemic (1957-1958) (73).

416 Notably, the re-analysis of COVID-19 epidemic curve from the initial cluster of cases
417 pointed out a substantial human-to-human transmission. It is opined that the common SARS-
418 CoV-2 (2019-nCoV) exposure history at Wuhan seafood market might have originated from
419 the human-to-human transmission rather than animal-to-human transmission (74). Meanwhile,
420 pointing out the zoonotic spillover in COVID-19 is too early to fully endorse (1). Following
421 the initial infection, human-to-human transmission has been reported with a preliminary
422 reproduction number (R_0) estimate of 1.4 to 2.5 (70, 75), and recently it is estimated to be
423 2.24 to 3.58 (76).In another study, the average reproductive number (R_0) of COVID-19 was
424 found to be 3.28, which is significantly higher than the initial WHO estimate of 1.4 to 2.5
425 (77). It is too early to obtain the exact R_0 value since there is a possibility of bias due to
426 insufficient data. The higher R_0 value is indicative of greater potential of the SARS-CoV-2
427 transmission in a susceptible population. That is not the first time where the culinary
428 practices of China have been blamed for the origin of novel coronavirus infection in humans.
429 Previously the animals present in the live-animal market were identified to be the
430 intermediate hosts of the SARS outbreak in china (78). Several wildlife species were found to
431 harbor potentially evolving coronavirus strains that can overcome the species barrier (79).
432 One of the main principles of Chinese food culture is that live-slaughtered animals are
433 considered to be more nutritious (5). This will increase the possibility of zoonotic disease
434 transmission to humans. Even though individuals of all ages and sexes are susceptible to
435 COVID-19, older people with an underlying chronic disease are more likely to become
436 severely infected (80). Recently, individuals with asymptomatic infection were also
437 considered as a source of infection to the other susceptible individuals (81). Both the
438 asymptomatic and symptomatic patients secrete similar viral load, which indicates that the
439 transmission capacity of asymptomatic or minimally symptomatic patients is very high. This
440 reflects that the transmission of SARS-CoV-2 (2019-nCoV) may occur early in the course of
441 infection (82). Atypical clinical manifestations have also been reported in COVID-19 in
442 which the only reporting symptom was fatigue. Such patients may lack the respiratory signs
443 such as fever, cough, and sputum (83). Hence, the clinician's must be on the look-out for the
444 possible occurrence of atypical clinical manifestations to avoid the possibility of missed
445 diagnosis. The early transmission ability of SARS-CoV-2 was found to be similar to or
446 slightly higher than the SARS-CoV, making it a controllable disease with moderate to high
447 transmissibility (84).

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Hence, the COVID-19 outbreak 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 repetition 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 coronavirus 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 (2019-nCoV) is from the Bat SARS-like Coronavirus, circulating in the Rhinolophus bat family (86).

Phylogenetic analysis of 10 whole-genome sequences of 2019-nCoV showed that they are related to two coronaviruses of bat origin, namely bat-SL-CoVZC45 and bat-SL-CoVZXC21 which were reported during 2018 in China (17). It was reported that angiotensin-converting enzyme 2 (ACE-2) receptor might be the binding spot for the virus (17, 87). 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 2019-nCoV 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). The immune response against Coronavirus is essential to control and eliminate 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 shed light on our understanding of the lung inflammation associated with this infection (24).

SARS is a viral respiratory disease caused by a previously unrecognized animal coronavirus that originated from the 'wet markets' in southern China after getting adapted to

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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). 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 data sets 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 play 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 (2019-nCoV) compared to its predecessors SARS might be the result of a stabilizing mutation 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 suggest a potential mechanism that differentiates from SARS (100). Even though the case fatality rates reported in COVID-19 is very low compared to the previous SARS and MERS outbreaks, it has so far caused more death than the SARS and MERS combined (101).

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 considered as the possible natural reservoir host of both SARS-CoV and MERS-CoV infection, while 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 possibility of adaptive mutation and recombination, may result in frequent interspecies transmission of coronavirus from bats

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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 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 conducted in 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 (2019-nCoV) 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, 2019-nCoV 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 (2019-nCoV) in familial clusters were 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). 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 (2019-nCoV) 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 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 sample 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 patients infected with COVID-19 (SARS-CoV-2) 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 coronaviruses is low, and it is not reported in either SARS or MERS (120).

The COVID-19 infection was associated with pneumonia, and some developed acute respiratory distress syndrome. 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). Middle-aged and elderly patients with underlying chronic diseases 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 acute respiratory distress syndrome (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-regulates 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

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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 coronavirus includes horses, camels, cattle, swine, dogs, cats, rodents, birds, ferrets, mink, bats, rabbits, snake, and several other wild animals (20, 30, 79, 93, 124, 125). 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 significant morbidity and mortality. Infection with PHEV also cause enteric infection but can cause encephalitis due to its ability to infect the nervous system (30).

Bovine coronaviruses (BoCoVs) are known to infect several domestic and wild ruminants (126). BoCoV inflicts 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 CoVsassociated 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 95% genomic similarity withhorseshoe bat (*Rhinolophus* sp.) coronavirus HKU2 suggesting bat origin of the pig virus (106, 134, 135). It is also important 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).

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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.

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 powered 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 batshad high commercial value since they are used in Traditional Chinese Medicine (TCM). Therefore, handling of bats for trading purposes poses a great risk of transmitting zoonotic coronavirus 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 major 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 coronavirus from Wuhan is a recombinant virus of the bat coronavirus and another origin-unknown coronavirus. The recombination was found to have occurred 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, indicating its origin to be from the bats (63).The involvement of bat-derived materials in causing the current outbreak cannot be ruled out. A high risk is involved in the production of bat-derived materials for TCM practices involving handling of wild bats. Use of bats for TCM practices will remain a serious risk for the occurrence of future zoonotic coronavirus epidemics (139). Furthermore, the pangolins are endangered species of animals that harboura wide variety of viruses, including coronaviruses (144). The coronavirus isolated from Malayan Pangolins (*Manis*

javanica) showed 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 (2019-nCoV). Comparison of the genomes suggests the possibility of recombination between Pangolin-CoV-like viruses with that of 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 of 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 harboured 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 close proximity to bat caves has earlier identified the serological evidence of SARS-related coronaviruses in humans. The people living at the wildlife-human interface mainly in rural China are constantly exposed to SARS-related coronaviruses (147). These findings will not have any significance until a major outbreak occurs due to a virus like SARS-CoV-2. Further studies are required to identify the possible animal reservoirs of 2019-nCoV, 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). 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 (2019-nCoV) specific nucleic acid detection kits. Also multiple laboratories are developing their own in-house RT-PCR. One among them is the SARS-CoV-2nucleic acid detection kit produced by Shuoshi Biotechnology (double fluorescence PCR method) (150). Nucleic acids of SARS-CoV-2 can be detected from the samples such as throat swabs (64), sputum, lower respiratory tract secretions, stool, and blood (80). 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). 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

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with unnecessary risks to the healthcare workers due to the close contact with patients (152). 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 result due to the possibility of faeco-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). 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 (2019-nCoV) nucleic acid using RT-PCR or by the identification of 2019-nCoV 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). In addition to all the above, sequencing and phylogenetic 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 great challenge due to 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 effective 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 detects the ORF1b and N regions of the SARS-CoV-2 (2019-nCoV) genome (156). That developed assay was found to achieve 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). 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).

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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 the 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 a period of 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).

VACCINES, THERAPEUTICS AND DRUGS

The recently emerged viruses such as Zika, Ebola and Nipah viruses and their high threats to the humans have paved race in exploring of designing and developing advanced vaccines, prophylactics, therapeutics, and drugs regimens to counter emergency viruses (161-163). Several attempts have been made to develop vaccines against coronavirus infection mostly by targeting the Spike glycoprotein. Nevertheless, due to the extensive diversity in antigenic variants, cross-protection provided 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).

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.

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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.This 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 the 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 wouldn't confer any detectable protection with the absence of detectable serum SARS-CoV-neutralizing antibodies (170). 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 S1 subunit is considered as the immunodominant region of the porcine deltacoronavirus S protein (171). Similary, 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 (2019-nCoV) 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 certain potential epitopes of S protein appear most promising vaccine candidates against coronaviruses in the near future. The RBD of the S1 subunit of S protein has a superior capacity to induce neutralizing antibody. 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 (2019-nCoV) 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-2 with 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 develop an effective vaccine against COVID-19. Immuno-informatics approach has been

used for the identification of important epitopes of cytotoxic T lymphocyte and B cell from surface glycoprotein of SARS-CoV-2 (2019-nCoV). 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 and they potentially induce immune responses (176). The recombinant vaccine can be designed by using rabies virus (RV) as a viral vector. The RVcan 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 programmes to develop SARS-CoV-2 vaccines (181). CEPI has a collaborative project with Inovio for designing MERS CoV DNA vaccine that could potentiate effective immunity. CEPI and 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 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).

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). 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).

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 to COVID-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.

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 (2019-nCoV), 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

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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 (2019-nCoV). 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 (2019-nCoV) 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.

Remdesivir, a novel nucleotide analogue 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 increasing the endosomal pH required 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 (2019-nCoV) associated pneumonia (197). This drug will be soon included in the next version of treatment guidelines issued by the National Health Commission of the People's Republic of China.

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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 the SARS-CoV-2 infection (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 intervention of disease in CoV exposed individuals. Patients recovering from SARS showed robust neutralizing antibodies against this CoV infectio (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 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 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 (2019-nCoV) for the cross-reactivity to occur.

Further evaluation is required before confirming the efficacy of such combination therapy. Development of broad-spectrum inhibitors against the often human coronaviral

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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. As 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.

Potential therapeutic agents

Therapeutic options that could be evaluated and utilized for against SARS-CoV-2 infection comprise of molecules binding to 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 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 might be of limited applicability and require trials against 2019-nCoV so as to gain practical usefulness. The binding of SARS-CoV-2 with ACE2 leads to exacerbation of pneumonia as a consequence of the imbalance in 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 inhibit the SARS coronavirus and human coronaviruses (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

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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 (2019-nCoV). 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 receptorsmay have the potentialfor 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) caninteract 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 an essential 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 (2019-nCoV), 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 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 were developed and now is in use for the evaluation of novel drugs and vaccines against MERS-CoV (220). In 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

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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).

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). 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 and 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 (2019-nCoV) 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).

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 personal protective equipment (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 reproduction number and reduce the transmission risk (228). 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. 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 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 cancelled 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 greatly to the spread of disease across the major cities of the world. Even though travel ban was hosted in Wuhan (89), infected persons who travelled 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 difficult 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 like 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 in the near future. 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 period of time? (**Fig. 7**).

CONCLUDING REMARKS

Several years after the global SARS epidemic, the current SARS-CoV-2/COVID-19 epidemic in China serves 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-2 (2019-nCoV) to 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 wildlifewith 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.

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 (2019-nCoV) was indeed expected. Similar to previous outbreaks, the current outbreak will also be contained in the near future. 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 period of 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 novel disease from becoming a pandemic.

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Author Biographies

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Kuldeep Dhama, is working as Principal Scientist in Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar-243 122, Bareilly, Uttar Pradesh, India (Born on 15th Aug., 1969). With 25 years of research and teaching experience in the areas of microbiology, immunology, virology, public health, medicine and biomedicine, as an eminent researcher, he has developed several diagnostics, vaccines, immunomodulatory modules and hypothesis to counter infectious diseases of animals, poultry and public health concerns. He has handled 20 Research Projects and Guided 17 MVSc/PhD scholars. With excellent academic records, he has to his credit 600 publications in scientific journals of repute, authored 06 books including Springer publisher, and 65 book chapters. Recently, Dr Dhama has been recognized as highly prolific author (extremely productive researcher) in "*Nature*" journal publication. He is a member of 20 professional/scientific societies, Fellow WRA (FWRA), and honored with 50 Best Paper Awards and other high recognitions/awards in the scientific arena; He has been awarded NAAS (National Academy of Agricultural Science, India) Associateship and worked as Nodal Officer, WTO; and Member, Wildlife Health Specialist Group (IUCN). He is actively serving as Editor-in-Chief, Co-Editor-in-Chief, Editor and Member, Editorial board of nearly 20 journals and peer-reviewer for several international journals of high repute. Guest edited six special issues of journals including CDM, VQ, IAD, JEBAS, IJP, AAVS. His Google scholar h-index is 45; Scopus h-index is 29.

Sharun Khan, M.V.Sc. Scholar, received his B.V.Sc. and AH degree from Kerala Veterinary and Animal Sciences University (KVASU), Pookode, Kerala, India, in 2018. Currently pursuing his M.V.Sc. degree in Veterinary Surgery and Radiology from the Indian Veterinary Research Institute (IVRI), Izatnagar, India, from 2018 onwards. He is working as a researcher in the Stem Cell Laboratory, Division of Surgery, IVRI. His area of interest is regenerative medicine with focus on understanding cell biology and molecular pathway involved in the maintenance and differentiation of stem cells originating from different tissues. Apart from his expertise in veterinary surgery and radiology, he has special interest and knowledge in the fields of veterinary medicine, pharmacology, infectious diseases of animals, wildlife diseases, diagnosis and therapy of animal diseases, nutrition and biomedicine. With excellent academic records, he has also received few awards and recognitions (fellowships and scholarships), and participated in several national and international workshops, training programs and courses. As a young researcher he has keen interest to learn good scientific writing skills, and has published 30 papers including in international journals of repute. He is highly enthusiastic to gain knowledge on the advancements in the educational and scientific research areas.

Ruchi Tiwari, is currently working as Assistant Professor in Department of Veterinary Microbiology, College of Veterinary Sciences, DUVASU, Mathura, India. She is currently pursuing her

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PhD. (Hons) degree from DUVASU, Mathura. With an excellent academic record and nine years of research and teaching experience, and expertise in the field of diagnosis, prevention and control of important livestock / poultry diseases and pathogens having public health significance along with special reference to veterinary microbiology, immunology, ethno-veterinary medicine, alternative and complimentary therapies, and bacteriophage therapy. She is currently working on antibiotic drug sensitivity studies and bacteriophage therapy. Her significant scientific contribution is reflected in her 150 research - review publications, 05 Book chapters. She has participated in 23 National and International Symposium – Conferences – Workshops - Seminars, and is Member/Life Member of 16 Professional/Scientific Societies. She has been honoured with Young Scientist Award, Best Paper Awards (10) and Outstanding Women Faculty Award (2019), She has been actively serving as Editor and Member, Editorial Board & Reviewer of 10 International Journals and Magazines of repute. She is Brand Ambassador of Bentham Science Publishers, UAE from July 2018 and recently selected as Fellow Member, World Researchers Associations (FWRA). Her Google scholar h-index is 37 (4830 citations); Scopus h-index is 26 (2298) citations.

Shubhankar Sircar, PhD scholar received his master's degree from Integral University Lucknow, India in 2012. He is now serving as Senior Research Fellow in an ICAR – National Fellow Scheme in the Division of Biological Standardization at the Indian Veterinary Research Institute (IVRI), Izatnagar, India. His area of interest is molecular epidemiology and genotype distribution of major enteric viruses with focus on developing different molecular as well as serological diagnostic testing assays. Apart from his expertise in viral diagnosis, he has special interest and knowledge in the fields of neglected viral, infectious diseases of farms animals and wildlife. With good academic records, he has also received a few awards and recognitions (Best poster and Young Scientist), and participated in several national and international workshops, training programs and conferences. As a young researcher he has published 30 papers in journals of repute. He is highly enthusiastic to gain knowledge on the advancements in the educational and scientific research areas.

Sudipta Bhat, a PhD scholar received his bachelors (B.V.Sc) from West Bengal University of Animal and Fishery Sciences, Kolkata, India and Masters (M.V.Sc.) from ICAR-Indian Veterinary Research Institute (IVRI), Bareilly, India. He is pursuing PhD degree in Veterinary Virology, ICAR-IVRI from 2016 onwards. He has worked on highly pathogenic H5N1 avian influenza virus and now working on emerging enteric viruses of zoonotic importance from different animal species. He has published his research findings in international journals. His area of interest is infectious diseases with focus on understanding antigenic and genetic diversity of viruses causing disease of several livestock species. With brilliant academic records, he has also been awarded with several fellowships and scholarships, and participated in several national and international workshops, training programs and courses.

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Yashpal Singh Malik, M.V.SC., PhD, Postdoc (USA), is an expert in enteric viral infections of animals and humans, zoonosis and emerging viral diseases. Since 2014, has been serving as ICAR-National Fellow and Professor of Veterinary Virology. His major research achievements include contributions in viral disease epidemiology, virus-host interactions, microbial biodiversity, characterization and diagnosis of animal pathogens. He did his postdoctoral (PDF) research in molecular virology at University of Minnesota, Saint Paul, USA (2001-2002). He acquired advanced training in molecular virology from University of Minnesota, Saint Paul, USA, Division of Virology, Ontario Research Institute, University of Ottawa, Ontario, Canada, And Wuhan Institute of Virology, China. He has been to the United States of America, Canada, United Arab Emirates, Malaysia, Belarus, Belgium, And People's Republic of China, and Sweden for representing India in scientific arena. He is Secretary General of Indian Virological Society (IVS) as well as Secretary (2020-2022) for the World Society for Virology (USA). He is Member of International Committee on Taxonomy of Viruses (ICTV) on *Birnaviridae* and *Picobirnaviridae* study group and a managing committee member of World Society for Virology (USA). He has authored 5 books of reputed publishers including ICAR, Elsevier and Springer Nature, and has published 218 scientific research articles, reviews in peer reviewed journals of high impact factor. His h index is 27 and RG score is 38.

Karam Pal Singh, Ph.D., obtained his B.V.Sc. & A.H. (1984) degrees from CSA University of Agriculture & Technology, Kanpur, India and his M.V.Sc. (1987) and Ph.D. (1990) degrees in Veterinary Pathology from the ICAR - Indian Veterinary Research Institute (IVRI), Izatnagar, India. Joined ICAR – IVRI in 1990 as Scientist (Veterinary Pathology) and worked there in the capacities of Scientist, Senior Scientist, and Principal Scientist before taking the charge of Acting Head, Division of Pathology on 1st January, 2019. Visited the Institute of Animal Health, Pirbright, U.K. as visiting fellow during April – December, 1996. Visited the Institute of Animal Health, Pirbright, U.K. as Post Doctoral Fellow on Wellcome Trust Fellowship during September 2002 to August, 2004. Further, visited the Veterinary Research Centre, Muscut, Sultanate of Oman, as Expert Pathologist during June 2008 to May 2009. Dr. Singh is a veterinary pathologist. His area of interest is infectious diseases with focus on understanding the pathogenesis and molecular diagnosis of viral diseases with particular reference to rabies and bluetongue.

Wanpen Chaicumpa, D.V.M. (Hons.), Ph. D. (Microbiology), is working as Emeritus Professor, Research Consultant and Head of the Center of Research Excellence on Therapeutic Proteins and Antibody Engineering, Department of Parasitology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, and consultant of the Faculty of

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Allied Health Sciences, Thammasat University, Thailand. She also serves as an executive member of the Thailand Academy of Sciences, and the Thailand Promotion of Sciences and Technologies foundation and consultant to the National Vaccine Institute, Thailand. She has served as Vice President on Academic Affairs, Mahidol University; Deputy Dean on Research and Academic Affairs, Faculty of Tropical Medicine, Mahidol University; Member of the National Research Council of Thailand (NRCT); Editor in Chief of Asian Pacific J Allergy & Immunology; Editorial board of several international scientific journals; Consultant to the deputy minister of public health, Thailand. Prof. Chaicumpa attended several short courses and visited several laboratories abroad and was appointed as consultant to the WHO, Geneva on the Control of Diarrhoeal Diseases program and the Food-borne Emerging Parasitic Infections. She was a consultant to the WHO Southeast Asian Regional Office, India, External auditor of The International Centre for Diarrhoeal Diseases Research of Bangladesh (ICDDR-B); Academic evaluator and invited professors to many universities abroad as well as Pasteur Institute in Paris. Prof. Chaicumpa received several Royal Decorations from His Majesty the King Rama 9 of Thailand. Internationally, she was the recipient of Women in Sciences Special Honor Award, UNESCO and L'OREAL and Asian Innovation Awards, Far Eastern Economic Review and Brain Power of Asia. She was recognized as an outstanding scientist of Thailand, outstanding researcher award / work of the year from the National Research Council of Thailand; outstanding research professor awards of the Thailand Research Fund; Chair Professor, National Sciences and Technology Development Agency (NSTDA); outstanding veterinarian award, The Veterinary Society of Thailand, etc. Her research interests include the study on intestinal immunity against enteric infections; vaccine development; immuno- and molecular diagnoses of tropical infections; allergy; immunotherapy and antibody engineering. She published more than 250 publications in international journals and own 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) and wrote several book chapters.

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

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President of the Travel Medicine Committee of the Pan American Infectious Diseases Association (API), as well as the Vicepresident of the Colombian Infectious Diseases Association (ACIN). He is member of the Committee on Tropical Medicine, Zoonoses and Travel Medicine of 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, has been recognized as Senior Researcher by the Ministry of Science in Colombia, MinCiencias. He is Professor of Medicine and Veterinary Medicine and Director of Scientific Research 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 H index is currently 29.

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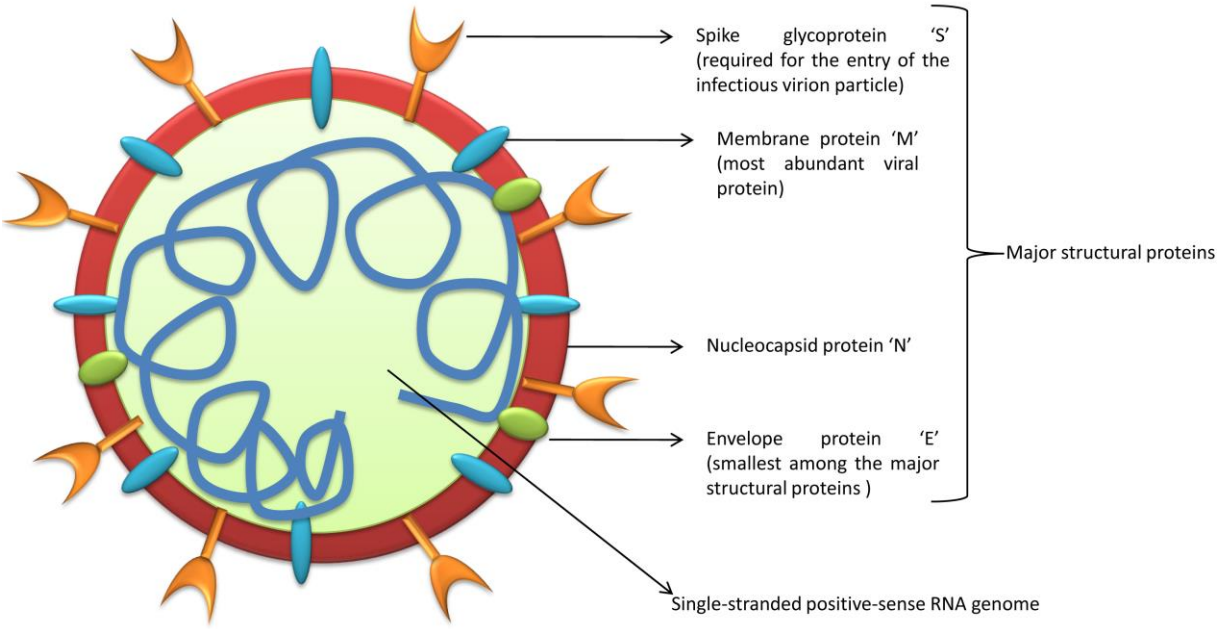

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2352 **FIG 1: 2019-nCoV virus structure**

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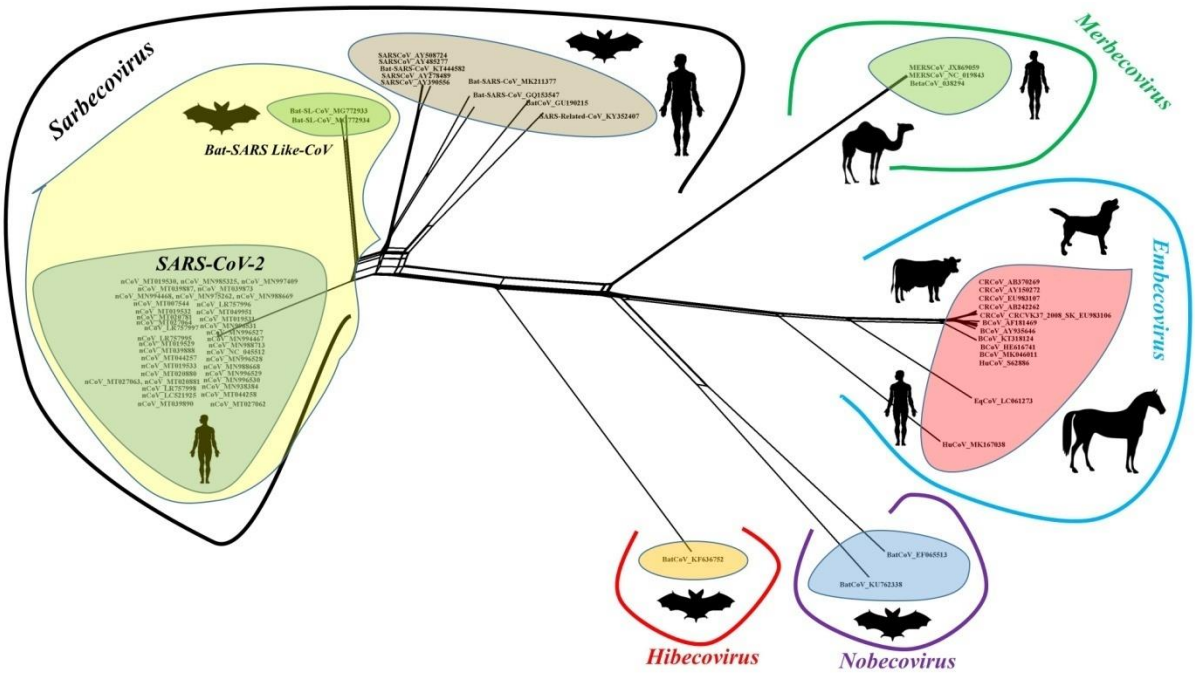

FIG 2: S-Gene Splits Tree Analysis: Spike (S) glycoprotein gene-based phylogenetic analysis (Splits-Tree 4.0) of SAR-CoV-2 isolates (39 isolates). The SARS-CoV-2 isolates analyzed with related CoVs from past human outbreaks and of animal-origin including MERS-CoV, bovine coronavirus, canine coronavirus, 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 world over. The nearest neighbours of SARS-CoV-2 are the Bat-SL-CoV, encircled in yellow colour.

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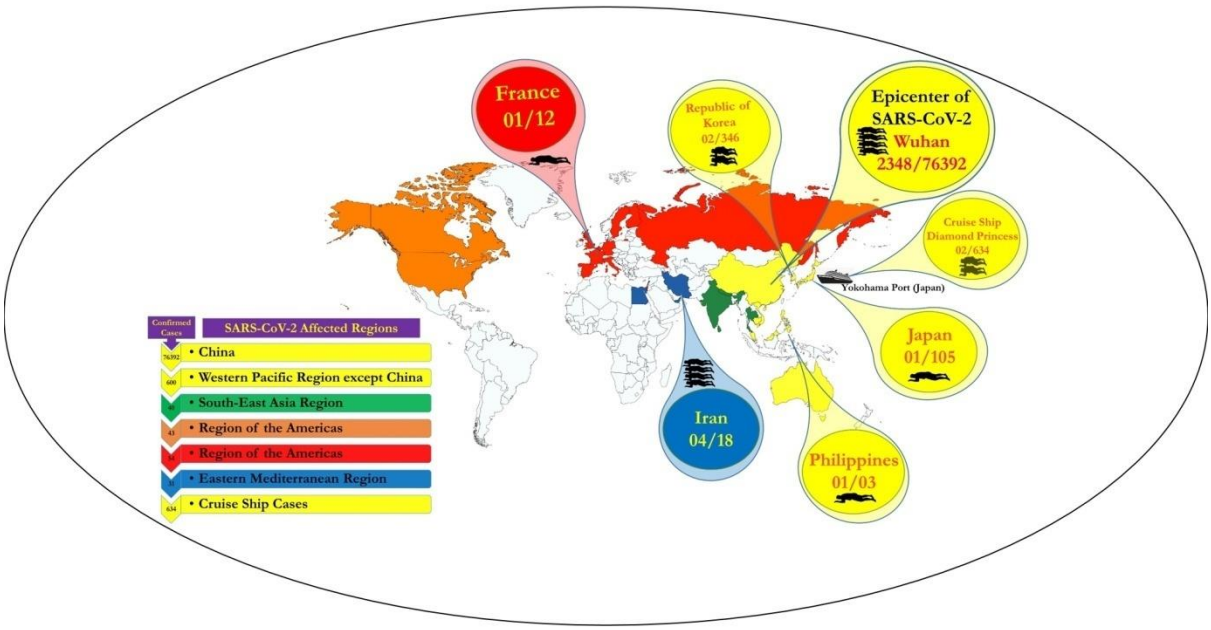

FIG 3: World Map depicting Current Scenario of 2019-nCoV, **affected countries and deaths: Countries, territories or regions with reported confirmed cases of SARS-CoV-2** 2019-nCoV/ **(February 22, 2020)**. Different colors indicate different geographical regions with the number of confirmed cases. In the table, region-wise total number of confirmed cases are depicted. Countries or regions with confirmed cases of deaths have been depicted in circled balloons.

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

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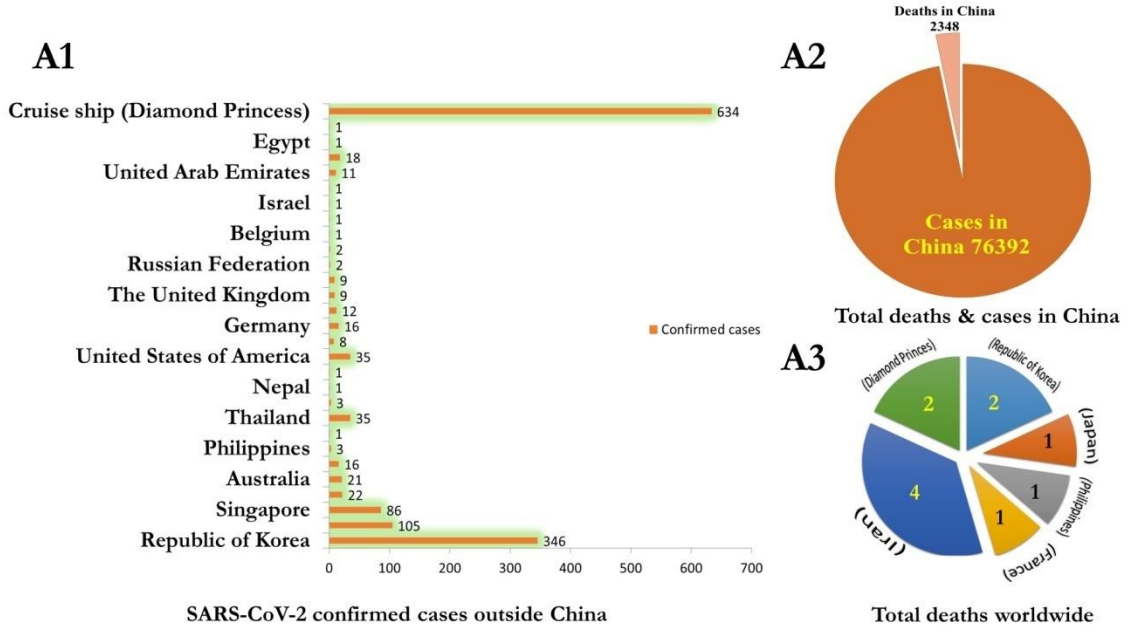

FIG 4: Bar graph and Pie chart for cases and deaths: Laboratory confirmed cases and deaths in China and world over due to SARS-CoV-2. A1) SARS-CoV-2 confirmed cases outside China which also includes the cruise ship *Diamond Princess* currently in Japanese territorial waters. **A2)** Total deaths and cases in China only; **A3)** Total deaths occurred world over other than China.

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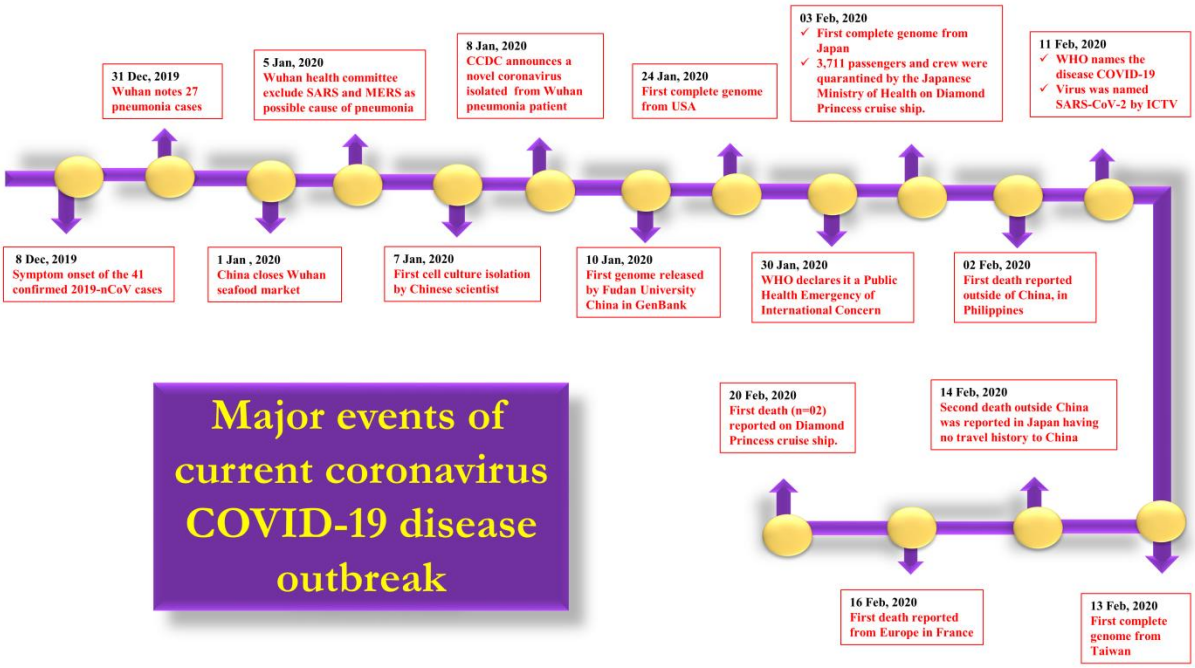

FIG 5: Timeline events of 2019-nCoV (SARs-2-CoV) / COVID-19 depicting the major events occurred during SARS-CoV-2/COVID-19 virus outbreak. The timeline describes the crucial events during the current SARS-CoV-2 outbreak starting from 8th Dec, 2019 and till 20 Feb 2020.

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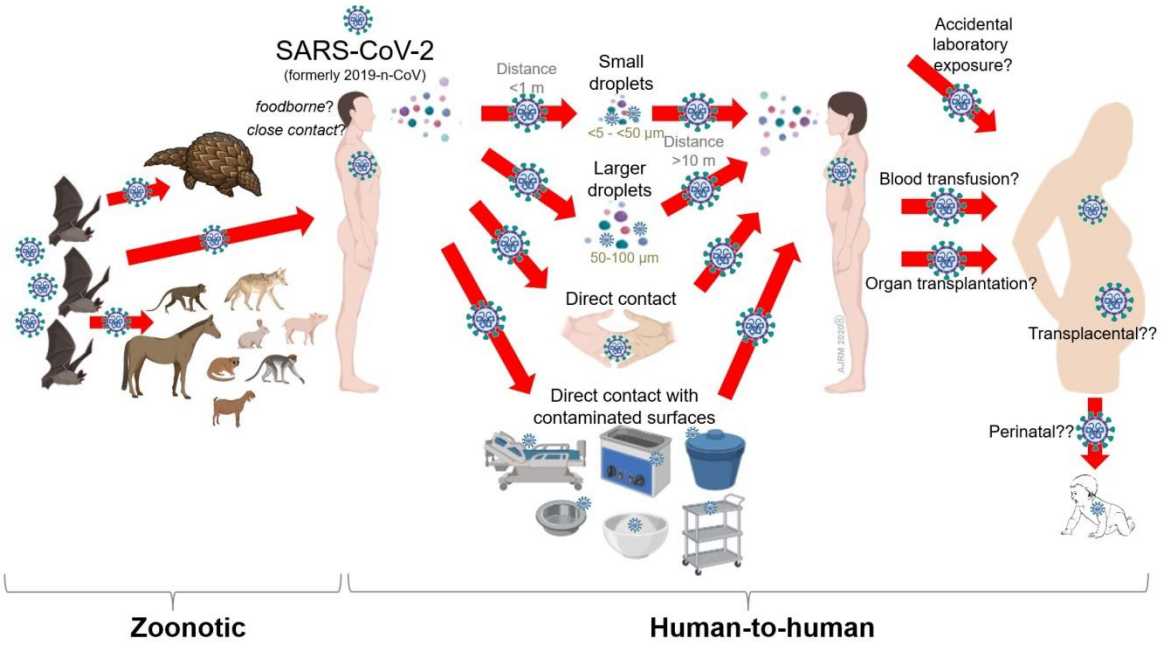

FIG 6: Potential transmission routes for SARS-CoV-2

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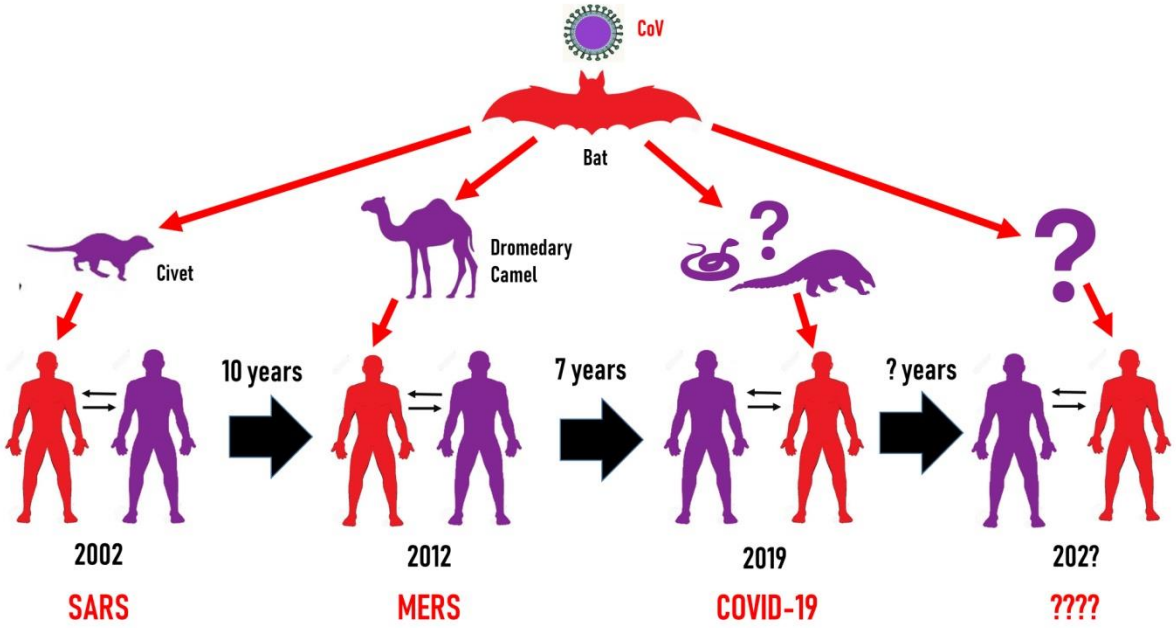

FIG 7: Coronaviruses origins. Coronavirus is the most prominent example of an emerging virus that has crossed the species barrier from wild animals to humans, like SARS and MERS. The origin of 2019-nCoV is also suspected to be from an intermediate animal host. The possibility of crossing the species barrier again for the fourth time cannot be ruled out.