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REVIEW ARTICLE

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Interspecies transmission of SARS CoV-2 with special emphasis on viral mutations and ACE-2 receptor homology roles

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ABSTRACT

COVID-19 outbreak was first reported in 2019, Wuhan, China. The spillover of the disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), to a wide range of pet, zoo, wild, and farm animals has emphasized potential zoonotic and reverse zoonotic viral transmission. Furthermore, it has evoked inquiries about susceptibility of different animal species to SARS-CoV-2 infection and role of these animals as viral reservoirs. Therefore, studying susceptible and non-susceptible hosts for SARS-CoV-2 infection could give a better understanding for the virus and will help in preventing further outbreaks. Here, we review structural aspects of SARS-CoV-2 spike protein, the effect of the different mutations observed in the spike protein, and the impact of ACE2 receptor variations in different animal hosts on inter-species transmission. Moreover, the SARS-CoV-2 spillover chain was reviewed. Combination of SARS-CoV-2 high mutation rate and homology of cellular ACE2 receptors enable the virus to transcend species barriers and facilitate its transmission between humans and animals.

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that sparked Coronavirus Disease 2019 (COVID-19) outbreak [1]. SARS-CoV-2 has the ability to infect a wide range of mammals [2]. Its detection in wild, zoo, farm and pet animals has evoked questions about its zoonotic, reverse zoonotic and panzootic transmissibility [2]. Zoonotic and reverse zoonotic transmission of SARS-CoV-2 could occur during common activities and interaction between humans and animals. A combination of the SARS-CoV-2 high mutation rate and the homology of cellular ACE2 receptors seem to enable SARS-CoV-2 to transcend species barriers and facilitate the viral transmission between humans and animals [3]. Therefore, studying susceptible, non-susceptible hosts, reservoirs and intermediate animals could give a better understanding for such virus and could help in predicting further outbreaks. Besides, hygienic, and biosafety measures that are aimed to decrease viral spread be further improved by such knowledge.

1.1. General properties of SARS-CoV-2

1.1.1. Morphology and structure of SARS-CoV-2

SARS-CoV-2 is an enveloped pleomorphic spherical virus and its size ranges from 50 nm to 140 nm. It has a crown appearance which shaped to from long club peplomers (20 nm) [4].

1.2. Genomic organization of SARS-CoV-2

Amongst all RNA viruses, coronaviruses have the largest RNA genome that is positive sense single strand RNA (+ssRNA) with SARS-CoV-2 having 29,903 bases and it encodes for 9860 amino acid residues [5]. The genome has two untranslated regions (UTRs) with lengths of (265) and (358) nucleotides at the 5′ and 3′, respectively [5]. ORF1ab is the largest ORF in the viral genome and it joins two others shorter ORFs (ORF1a and ORF1b). ORF1ab overlaps with ORF1a, and the translation of the latter produces the shorter polypeptide (pp1a). Ribosomal frameshift occurs at the – 1 position, upstream of the ORF1a stop codon, allowing the translation of ORF1b to be continued, and hence yielding a longer polypeptide

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(pp1ab). This chain is then cleaved into a number of non-structural proteins. The switch between the expression of the two polypeptides is regulated by a mechanism known as – 1 programmed ribosomal frameshifting (–1 PRF) [6]. This mechanism is controlled by an RNA element (a pseudoknot) that directs the ribosome to shift the reading frame via one base essentially bypassing the stop codon at the end of ORF1a, and the full expression of pp1ab polypeptide. This mechanism is utilized by both SARS-CoV-2 and SARS-CoV, and the regulatory RNA element in both viruses have similar structure and mechanism. Mutations that alter the structure of the pseudoknot inhibit viral replication [7]. The cryo-EM structure of pseudoknot had been determined both in the free form [8] and along with the ribosome during translation [9]. The polypeptides that are eventually expressed encode for 16 non-structural proteins (NSPs) in SARS-CoV-2 genome. These NSPs include two proteases (NSP3 and NSP5), polymerases, helicases, endoribonucleases, and ribonucleases [5].

NSP3 is a Papain-like protease (PLpro) that is located between positions (Ala 819-Gly 2763) with a length of 1,944 amino acids and NSP5 is a Chymotrypsin-like protease or 3C-like proteinase (3Clpro) or main protease (Mpro) which is located between positions (Ser 3264-Gln 3569) with a length of 305 amino acids. Plpro cleaves the viral polyprotein at three regions that has a sequence consensus "LXGG↓XX". PLpro is involved in viral maturation, replicase-transcriptase complex assembly, evasion host immune responses and it has interferon antagonist (IFN) effect [10]. 3Clpro is the main protease that cuts 11 sites in viral polyproteins 1a/1b with sequence consensus X-(L/F/M)- Q↓(G/A/S)-X[11,12]

Another NSP is the RNA-dependent RNA polymerase (NSP12) which is located between (Ser 4393-Gln 5324) with 931 amino acid length [13]. Its main role is viral replication and transcription [14–17]. The helicase enzyme (NSP13) is located between positions Ala 5325-Gln 5925 with a length of 600 amino acid and it has a RNA 5' triphosphatase activity [15,18]. Endoribonuclease enzyme (NSP15) is positioned between (Ser 6453-Gln 6798) with a length of 345 amino acids and it has endoribonuclease enzymatic activity which helps the virus to evade host immune response [19,20]. Additional NSPs that regulate genomic transcription, viral replication and host immune response suppression/evasion are also present in SARS-CoV-2 genome [5].

Besides NSPs, the viral genome encodes for structural proteins (SPs) which include nucleocapsid (N), spike glycoprotein (S), envelope protein (E) and membrane protein (M) [4]. The genomic organization of SARS-CoV-2 is tabulated in Table 1.

The table lists known and predicted ORFs in SARS-CoV-2. The major functions of the various viral proteins are also tabulated. Nucleotide positions refer to the Wuhan strain.

1.3. Physical, chemical and biological properties of SARS-CoV-2

SARS-CoV-2 can survive in aerosols without ventilation for 3 hours [35] and it is more stable on smooth surfaces such as glass, steel and plastic (for many days) than on rough surfaces such as paper, wood, and fabric (only for several hours) [36]. SARS-CoV-2 is stable at 4°C and low pH (up to 3), but sensitive to UV radiation and it is heat labile (inactivated in 5 minutes at 70°). Furthermore, lipid solvents such as soap, ethanol, chlorine-containing disinfectant, ether and chloroform can efficiently inactivate this virus. It is also sensitive to formalin, non-ionic detergents (tween), and oxidizing agents [36,37].

1.4. SARS-CoV-2 replication cycle:

The first step of SARS-CoV-2 replication cycle is the attachment between the virus spike protein and the host receptor. More specifically, the spike protein contains the viral receptor binding domain (RBD) which directly binds with host angiotensin-converting enzyme 2 cell receptors (ACE2) [1,38]. ACE2 has been found in human cells present in various tissues and organs including nasal, oral and gastrointestinal tract mucosa, as well as, in lung, liver, kidneys and brain cells [39]. After RBD/ACE2 binding, the virus gains access to the cellular cytoplasm through the proteolytic activity of the host proteases eventually leading to the cleaves the viral spike glycoprotein into S1 and S2 [40], and entry into the cell by fusion. Following the virus-receptor binding, two proteolytic activities are required for the SARS-CoV-2 spike protein activation and virus entry into cells [41]. The two cleavage events eventually lead to large conformational changes in the viral protein allowing the exposure of the otherwise inaccessible fusion peptide, and hence allowing fusion to occur [42,43]. The first cleavage is by furin, while the second is carried out by Transmembrane serine protease 2 (TMPRSS2). Furin is a Type I transmembrane protein with its transmembrane domain that adopts an Nout-Cin orientation, and to date proven to be active for SARS-CoV-2 only. Furin cleaves the S1/S2 boundary site at a multibasic site (proline – arginine–arginine – alanine residues, known as PRRA), which results in the subsequent detachment of the S1 from the S2 subunit. Unlike SARS-CoV-2, SARS-CoV enters cells via endocytosis and requires cathepsin B and L in lysosomes for entry [44–46]. Similarly, MERS-CoV requires cathepsin L for viral entry [47].

TMPRSS2 on the other hand, is a host protease that is also involved in the processing and cleavage of the

Table 1. Genomic organization of SARS-CoV-2.

	Region	Location	Length	Function
1	**ORF1a (ORF1a polyprotein)**	**266 to 13,468**	**13202 nt (4400 AA)**	
	NSP1	(1 Met-Gly 180)	180 AA	Target the translation machinery in host cell and it has immune suppressor action [5,21–23]
	NSP2	(181 Ala-Gly 818)	638 AA	Unknown.
	NSP3 (Papain-like protease) (PLpro)	(819 Ala-Gly 2763)	1944 AA	PLpro cleaves viral polyprotein at 3 regions "LXGG ↓ XX" for viral maturation, replicase-transcriptase complex assembly, evade host immune responses and it has interferon antagonist (IFN) effect [5,10].
	NSP4	(2764 Lys-Gln 3263)	499 AA	Complex with nsp3 and nsp6 forming double membrane vesicles (DMV) and involved with Nsp3, nsp4 and nsp6 to convert host endomembranes into replication organelles [5,24–26].
	NSP5 (Chymotrypsin-like protease) or (3C-like proteinase) (3CLpro) or (main protease) (Mpro)	(3264 Ser-Gln 3569)	305 AA	The main protease cuts 11 sites in viral polyproteins 1a/1b with sequence consensus X-(L/F/M)- Q ↓ (G/A/S)-X[5,11,12].
	NSP6	(3570 Ser-Gln 3859)	289 AA	Complex with nsp3 and nsp4 forming double membrane vesicles (DMV) and involved with Nsp3, nsp4 and nsp6 to convert host endomembranes into replication organelles [5,24–26].
	NSP7	(3860 Ser-Gln 3942)	82 AA	Primase, combine with NSP8 and act as cofactors for NSP12 (RdRp) to conserve the viral structure [5,17,27,28].
	NSP8	(3943 Ala-Gln 4140)	197 AA	Primase, combine with NSP7 and act as cofactors for NSP12 (RdRp) to conserve the viral structure [5,17,27,28].
	NSP9	(4141 Asn-Gln 4253)	112 AA	Single-stranded RNA binding activity [5,15].
	NSP10	(4254 Ala-Gln 4392)	138 AA	Cofactor for nsp14 and nsp16 for replication fidelity [5,29].
	Nsp11		7 AA	—
(Ribosomal frameshift at −1 of ORF 1b, i.e. at vRNA position 13,468)				
2	**ORF1b**	**13442 to 21,562**	**8121 nt (2696 AA)**	**ORF1b is expressed as part of polypeptide 1ab (pp1ab).**
	NSP12 (RNA-dependent RNA polymerase) "RdRp"	(4393 Ser-Gln 5324)	931 AA	Viral replication and transcription [5,14–17].
	NSP13 (Helicase)	(5325 Ala-Gln 5925)	600 AA	Helicase and has RNA 5′ triphosphatase activity [5,15,18].
	NSP14	(5926 Ala-Gln 6452)	526 AA	RNA cap formation, N7-methyltransferase, 3′ to 5′ exoribonuclease with proofreading activity [5,30–32].
	NSP15 (Endoribonuclease)	(6453 Ser-Gln 6798)	345 AA	Endoribonuclease enzymatic activity that helps the virus to evade from immune response [5,19,20].
	NSP16	(6799 Ser-Asn 7096)	297 AA	RNA cap formation and 2′ - O- methyltransferase [5,33,34].
3	Spike (Spike glycoprotein)	21563 to 25,384	3821 nt (1273 AA)	Initiates ACE2 receptor attachment and interacts with neutralizing antibodies [5]
4	ORF3a (NSP3a)	25393 to 26,220	827 nt (275 AA)	Accessory factor [5]
5	ORF3b (NSP3b)	25765 to 26,220	455 nt (151 AA)	Unknown
6	E (Envelope protein)	26245 to 26,472	227 nt (75 AA)	Has a crucial role in viral assembly and release [5]
7	M (Membrane protein)	26523 to 27,191	668 nt (222 AA)	Assembly and budding [5]
8	ORF6 (NSP6)	27202 to 27,387	185 nt (61 AA)	Unknown
9	ORF7a (NSP7a)	27394 to 27,759	365 nt (121 AA)	Unknown
10	ORF7b (NSP7b)	27756 to 27,887	131 nt (43 AA)	Unknown
11	ORF8 (NSP8)	27894 to 28,259	365 nt (121 AA)	Unknown
12	N (Nucleocapsid protein)	28274 to 29,533	1259 nt (419 AA)	RNA synthesis, transcription and virus budding [5]
13	ORF9a (NSP9a)	28284 to 28,577	293 nt (97 AA)	Unknown
14	ORF9b (NSP9b)	28734 to 28,955	221 nt (73 AA)	Unknown
15	ORF10 (NSP10)	29558 to 29,674	116 nt (38 AA)	* There is no evidence that this protein is expressed or plays any role in pathogenesis and transmission [5].

spike protein. TMPRSS2 is a Type II transmembrane protein with its transmembrane domain adopts an Nin-Cout orientation [48,49], and mainly present on the surface of lung cells. That cleavage process is associated with the S protein membrane fusion and is essential for both SARS-CoV and SARS-CoV-2 [42]. Specifically, TMPRSS2 cleaves the S2 protein subunit of the Spike, after its detachment from the S1. The cleavage occurs near the N-terminal of the S2 [50], at a site known as the S2' site. The latter cleavage leads to the exposure of the internal fusion peptide which plays a critical role in membrane fusion [51]. The two heptad repeats domains (HR1 and HR2) of the S2 structurally rearrange to form a six-helix bundle (6HB) fusion core that brings the virus particle membrane closer to the host cell membrane [52–55], and then fusion occurs. TMPRSS2 is also involved in the cleavage of the viral receptor (ACE2), inducing the shedding of the ACE2 and hence aiding in the subsequent uptake of the virus [56].

The second stage is viral entry via fusion at endosomal or cellular membranes, then, uncoating occurs and viral positive sense single stranded RNA (+ssRNA) genome is released into host cytoplasm [38]. Consequently, viral +ssRNA is immediately translated into 2 polyproteins (pp1a and pp1ab). These 2 polyproteins undergo autoproteolysis and co-translational cleavage to generate NSPs which form replication/transcription complex. A safe microenvironment (perinuclear double-membrane vesicles "DMVs", convoluted membranes "CMs", and small open double-membrane spherules "DMSs") is formed to protect replication and transcription of subgenomic mRNAs (both negative and positive sense). Double-membrane vesicles (DMVs) are modified endoplasmic reticulum membranes that have been associated with SARS-CoV-2 replication. Recent studies showed that abundant viral RNA synthesis is associated with DMVs in infected cells only [57]. This proposed that the virus takes DMVs as Replication organelles (RO), shielding its dsRNA intermediates in these DMVs, which may lead to evading IFN-1 activation [58].

In addition to acting as a template for the polypeptides, the +ssRNA also serves as a template for the synthesis of the negative-sense RNA intermediates. Subsequently, the latter serves as a template for replication via the synthesis of both the gRNA and for the subgenomic RNAs (sgRNAs). Whereas the gRNAs are assembled into the newly formed virions, the 5' capped and polyadenylated [59,60] sgRNAs are directly translated. Both gRNA and sgRNA carry a common leader sequence of about 65 to 95 nucleotides in length. Studies have shown that the sgRNAs encodes for major structural proteins (S, M, N and E) and other accessory proteins (ORF3a, ORF6, ORF7a, ORF7b, ORF8 and ORF10) [15,61,62]. The former nine sgRNAs had been confirmed while ORF10 remains questionable and still needs further investigation. Moreover, non-canonical sgRNAs as well as RNA modifications at specific sites had been proposed [62].

Hence, the third step is the translation of the subgenomic mRNA into structural protein (Spike "S", Membrane "M", Envelop "E" and Nucleocapsid "N"). Finally, the nucleocapsid buds into the Endoplasmic Reticulum – Golgi Intermediate Compartment (ERGIC) studded and assembled with S, M and E proteins. Eventually, virions are formed and transported to the cellular surface via vesicles, then viral shedding from the host cell occurs via exocytosis releasing infectious virions [38].

1.5. The structure of spike glycoprotein

The spike glycoprotein consists of 1273 amino acids that is shaped into 2 subunits (S1 and S2), as illustrated in Figure 1 [5]. The S1 subunit consists of four primary regions; two of them are critical for viral binding with host antibodies (the N-terminal domain "NTD" which is composed of 292 amino acids and the receptor binding domain "RBD" that carries receptor-binding motif "RBM", which is 210 amino acids long) [63]. Besides, RBD mainly bind host ACE2 receptors [64]. The other two regions of the subunit S1 are the C-terminal domains 1 (CTD1) (64 amino acids) that involved in host immune evasion [64] and the C-terminal domains 2 (CTD2, 96 amino acids) affect stability of spike trimer [65].

The S2 subunit on the other hand, consists of six main regions including the fusion peptide (FP, 18 amino acids), the fusion peptide proximal region (FPPR, 77 amino acids), heptad repeat 1 (HR1) motif (76 amino acids), the central helix (CH, 51 amino acids), a β-hairpin (34 amino acids), and heptad repeat 2 (HR2) motif (49 amino acids) that is followed by the transmembrane (TM) region (24 amino acids) and the intracellular region (IC, 41 amino acids) [66,67].

The S1 subunit protects the viral fusion apparatus [68] and it switches between open-standing up (RBD-up) and closed-down (RBD-down) conformations to bind with cellular ACE2 receptors [69,70]. After the spike attachment, separation of S1 occurs and S2 undergoes a rearrangement process to proceed to viral fusion [68–71].

The upper panels (panels A and B) show SARS-CoV-2 structure and its entry that includes (spike/ACE2 binding, cleavage of S protein, Activation of S2 domain, and fusion). The spike protein cartoon was generated from PDB ID 6×r8[72]. The lower panel (panel C) illustrates a schematic representation of the spike protein gene. The domains and regions in the three panels are depicted by the same colouring scheme, using the Wuhan strain as a reference (Reference Sequence NC_045512.2, Gene ID:

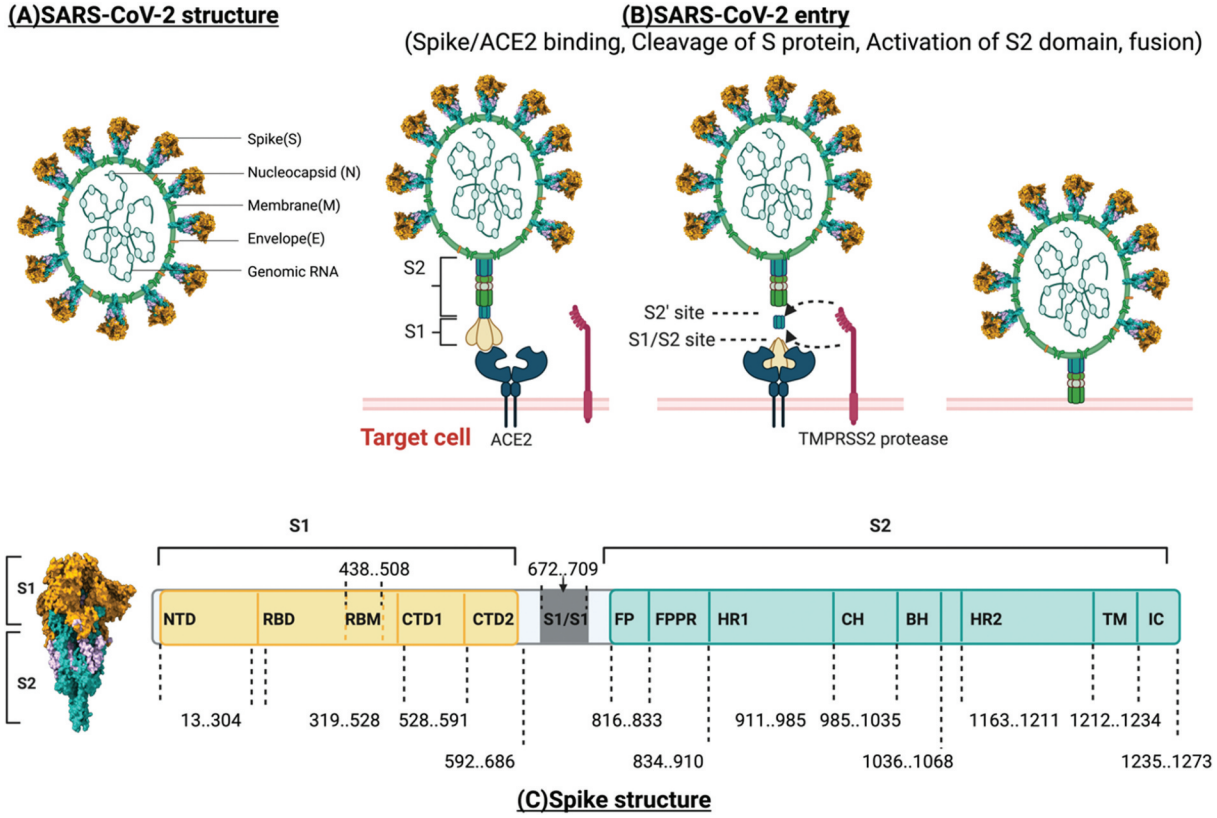

Figure 1. SARS-CoV-2 structure, entry, and the structure of the spike protein gene.

43740568) [66,67]. The figure was generated by using Biorender website [73] and ChimeraX [74].

2. SARS-CoV-2 taxonomy and variants classification

SARS-CoV-2 belongs to genus Betacoronavirus "β-coronavirus" in Coronavirinae subfamily that is a member of Coronaviridae family in Nidovirales order. In details, there are four genera in Coronaviridae family: α-coronavirus, β-coronavirus, γ-coronavirus and δ- coronavirus. Particularly, β-coronavirus genus is sectioned to (a, b, c and d) lineages and SARS-CoV-2 belongs to b- lineage. SARS-CoV-2 shares 80% nucleotide similarity with SARS-CoV-1 [1].

2.1. Tracking SARS-CoV-2 variants

Like many RNA viruses, SARS-CoV-2 has mutated rapidly by time, with an approximate rate of $1.5–3.3 \times 10^{-3}$/per site/year [75]. Some of these acquired mutations have an impact on viral transmission, diagnosis, disease severity, vaccines, and therapeutics efficacy. Clearly, and despite its small size, the RBD domain shows a higher mutation frequency compared to the average mutation frequency in the other parts of the spike protein.

Since January 2020, the World Health Organization (WHO) has been monitoring the evolution of SARS-CoV-2. Specific SARS-CoV-2 variants were categorized as Variant of Concern (VOC), Variant of Interest (VOI), and Variant Under Monitoring (VUM). The classification is aimed to clarify the significance of viral amino acid substitutions to take necessary actions that would reduce the viral spread [76]. The WHO has updated the previous categories to remove Variant Under Monitoring (VUM) and replaced it with Formerly monitored variants (FMV) [77]. Therefore, countries were encouraged to increase their capacity for sequencing and surveillance to detect any abnormal epidemiological events [76,77]. Definitions and examples for different categories of SARS-CoV-2 variants are tabulated in Supplementary Table 1.

2.2. Different nomenclature systems for SARS-CoV-2 variants

There are many proposed nomenclature systems for SARS-CoV-2 variants. The most used in the literature are the Pango lineage, Nextstarin, GISAID clades and WHO nomenclatures. Knowing how the different systems of naming SARS-CoV-2 work would make it easier to trace SARS-CoV-2 evolution and its subsequent spread.

2.2.1. Pango lineage nomenclature

This nomenclature has been generated from thousands of analysed SARS-CoV-2 genome sequences. It

is a dynamic and rational nomenclature system which uses a phylogenetic framework to detect viral lineages. This system has helped in understanding and tracking SARS-CoV-2 patterns globally [78,79].

2.2.2. Nextstrain nomenclature

This system named SARS-CoV-2 variants by using both alphabets and years (19A, 19B, 20A, 20B, 20C, 20D, 20E, 20F, 20 H, 20I, 20J, 21A, 21B, 21C, 21D, 21F, 21 G, 21 H, 21K, 21 L, 21 M, 22A, 22B and 22C) [80].

2.2.3. GISAID clades nomenclature

This system classifies SARS-CoV-2 variants into large clades in the context of marker variants related to Wuhan (WIV04) – SARS-CoV-2 reference virus and it is classified into 10 clades (S, L, V, G, GH, GV, GR, GRY, GK and GRA) [81] as illustrated in Table 2.

2.2.4. WHO nomenclature

The WHO suggests an easy-to-pronounce nomenclature system for non-scientific audiences and it has recommended using Greek letters (Alpha, Beta, Gamma, Delta, Epsilon, Zeta, Eta, Theta, Iota, Kappa, Lambda, Mu and Omicron) [77]. SARS-CoV-2 different nomenclature systems with spike mutations and epidemiology are demonstrated in Table 3. Those mutations were mapped to a surface representation of the spike protein structure (Supplementary Figure S1). It is clear from Supplementary Figure S1 that the virus had accumulated many surface mutations during its course of evolution from the initial Alpha variant to the Omicron variants.

2.3. Different SARS-CoV-2 spike mutations and their effects

Major mutations and changes in the amino acids of the spike protein that lead to changes in the surface hydrophobicity and polarity could affect viral infectivity and pathogenicity, as well as facilitate viral transmission between the different species [69]. It is possible that frequent amino acid mutations have a role in host adaptation [64]. Different SARS-CoV-2 mutations referenced to Wuhan virus, their positions and their effects are tabulated in Table 4 and illustrated in Figure 2 which showed the overall distributions of spike mutations among different SARS-CoV-2 variants. Furthermore, Figure 3 displays frequency of spike mutation in the different variants.

The figure shows the spike protein mutations in all strains with respect to its receptor. The protein is shown as an isosurface and the ribbon for a single monomer (including its RBD) is shown in dark grey. Residues that had undergone mutations in all strains are shown in red spheres, and receptor is in cyan.

The figure displays frequency of the spike protein mutations in SARS-CoV-2 variants including the most dominant mutation (D614G) followed by the mutation at position 484 which has different residue substitutions (E484K, E484Q and E484A).

3. Spillover and zoonotic transmission of coronaviruses

Generally, coronaviruses affect multiple species including poultry, humans and other mammals [124]. Seven coronaviruses have the ability to infect humans, all of which have non-human precursors [125]. Four of these human coronaviruses (HcoV) (NL63, 229E, OC43, and HKU1) cause common cold with mild or asymptomatic respiratory signs [126–128]. These 4 viruses are thought to have bat or rodents origin [125,129], though further evidence are needed to verify such claim. The other three HcoV cause severe respiratory signs including Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) which first appeared in 2002, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 and SARS-CoV-2 in 2019. All of the mentioned viruses are thought to have bat origin [2].

Particularly, SARS-CoV was detected in horseshoe bats with 99.8% similarity with human SARS-CoV isolates, thus, bats are proposed to be the natural precursors for SARS-CoV [130–133]. SARS-CoV antibodies were detected in raccoon dogs and masked palm civets in wet markets [130,134,135] and they could act as intermediate hosts [125,136]. MERS-CoV had infected 2,562 individuals, resulting in 881 deaths [137]. Indeed, most of the latter individuals had been in contact with dromedary camels and the MERS-CoV isolates from camels had high sequence identity with MERS-CoV human isolates [138,139]. MERS-CoV was also detected in 14 bat species [140] with 85% sequence identity with the isolates from humans or camels [141]. Therefore, these findings had proposed that bats could be also the natural host for MERS-CoV [142,143]. SARS-CoV-2 that caused the recent pandemic has also been reported as a zoonotic disease [144–146].

4. The proposed spillover chain of SARS-CoV-2

There had been several hypotheses about SARS-CoV-2 spillover chain, including the original hypothesis which proposed that bats and pangolins may be the natural precursors for SARS-CoV-2. Furthermore, other partners may be included in this chain such as minks. Moreover, there are concerns about the role of mice in the emergence of Omicron-SARS-CoV-2 variant and SARS-CoV-2 transmission via food and food packaging. The prospective role of the previous contributors to the SARS-CoV-2 spillover chain

Table 2. GISAID clades, Pango lineages with key amino acid substitutions and reference clades [81].

	GISAID Clades	Pango lineages	Key amino acid substitutions	Reference clade
1	S	A	(C8782T, T28144C, NS8-L84S).	hcov-19-Guangdong-EPI-ISL-403932–14 January 2020
2	L (Wuhan)	B	(C241, C3037, A23403, C8782, G11083, G25563, G26144, T28144, G28882)	hcov-19-Wuhan-WIV04-EPI-ISL-402124–30 December 2019
3	V	B.2	(G11083T, G26144T, NSP6-L37F + NS3-G251V).	hcov-19-Italy-EPI-ISL-412974–29 January 2020
4	G	B.1	(C241T, C3037T, A23403G, Spike-D614G).	hcov-19-Germany-EPI-ISL-406862–28 January 2020
5	GH	B.1	(C241T, C3037T, A23403G, G25563T, Spike-D614G + NS3-Q57H).	hcov-19-Canada-EPI-ISL-418345–2020–02
6	GV	B.1.177	(C241T, C3037T, A23403G, C22227T, Spike-D614G + Spike-A222V).	hcov-19-Spain-EPI-ISL-539548–26 June 2020
7	GR	B.1.1.1	(C241T, C3037T, A23403G, G28882A, Spike-D614G + N-G204R).	hcov-19-England-EPI-ISL-466615–16 February 2020
8	GRY (Alpha)	B.1.1.7	(C241T, C3037T, 21765–21770 del, 21991–21993 del, A23063T, A23403G, G28882A, Spike-H69 del, Spike-V70 del, Spike-Y144 del, SpikeD614G, N-G204R, Spike-N501Y).	hcov-19-England-EPI-ISL-601443–20 September 2020
9	GK (Delta)	B.1.517.2	(C241T, C3037T, A23403G, C22995A, Spike-D614G + Spike-T478K).	hcov-19-India-EPI-ISL-1663515–12 December 2020
10	GRA (Omicron)	B.1.1.529 + BA	(C241T, C3037T, A23403G, G28882A, Spike-D614G, N-G204R, + (at least 6 of the following amino acid changes in the Spike: V143del, Y145del, N211del, ins214EPE, G339D, S371L, S477N, T478K, E484A, Q493R, Q498R, T547K, N679K, P681H, P681R, N764K, D796Y, N856K, Q954H, N969K, L981F).	hCoV-19/South Africa-EPI-ISL-7456440–5 November 2021

Table 3. SARS-CoV-2 variants with different proposal nomenclature systems with key spike mutations [76,80,82].

No.	WHO	Pango	Nextstrain	GISAID	First location	Emergence	Key spike mutations
1	Alpha, V1	B.1.1.7	20I	GRY	UK	September 2020	H69-, V70-, Y144-, N501Y, D614G, P681H
2	Beta, V2	B.1.351	20H	GH/501Y	South Africa	May 2020	L18F, K417N, E484K, N501Y, D614G, A701V
3	Gamm, V3	P.1	20J	GR/501Y	Brazil	November 2020	L18F, P26S, K417T, E484K, N501Y, D614G, H655Y
4	Delta, V4	B.1.617.2	21A	G/478K	India	October 2020	T19R, L452R, T478K, D614G, P681R, D950N
5	Epsilon	B.1.427, B.1.429	21C	GH/452R	USA	March 2020	S13I, W152C, L452R
6	Eta	B.1.525	21D	G/484K	Multiple countries	December 2020	A67V, H69-, V70-, Y144-, E484K, D614G
7	Iota	B.1.526	21F	GH/253G	USA	November 2020	T95I, D253G, E484K, D614G, A701V
8	Kappa	B.1.617.1	21B	G/452R	India	October 2020	L452R, E484Q, D614G, P681R
9	Lambda	C.37	21G	GR/452Q	Peru	December 2020	D253N, L452Q, D614G
10	Mu	B.1.621	21H	GH	Colombia	January 2021	T95I, Y144S, Y145N, E484K, N501Y, D614G, P681H, D950N
11.1	Omicron	BA.1	21K	GR/484A	South Africa	November 2021	A67V, H69-, V70-, T95I, G142-, Y144, Y145D, G339D, S371L, S373P, S375F, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K
11.2	Omicron	BA.2	21L	GR/484A	Multiple countries	December 2021	T19I, L24-, P25-, P26-, A27S, G142D, V213G, G339D, S371L, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K
11.3	Omicron	BA.4, 5	22A, 22B	GR/484A	Multiple countries	April 2022	T19I, L24-, P25-, P26-, A27S, H69-, V70-, G142D, V213G, G339D, S371L, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K
11.4	Omicron	BA.2.12.1	22C	GR/484A	Multiple countries	June 2022	T19I, L24-, P25-, P26-, A27S, G142D, V213G, G339D, S371L, S373P, S375F, T376A, D405N, R408S, K417N, N440K,L452Q, S477N, T478K, E484A, Q493R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, Q498R L452Q, S477N, T478K, E484A, Q493R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, Q498R

Table 4. Different SARS-CoV-2 spike protein mutations referenced to Wuhan virus, their position, and their effect.

	Mutations referenced to Wuhan virus	Position	Mutation effect	Notes
1	S:L18 • S:L18F • S:L18P	NTD	• It could decrease the viral binding affinity with NTD monoclonal antibody [63].	• S:L18F is found in Beta and Gamma variants [83].
2	S:H69-	NTD	• This amino acid deletion was detected many, thus, it was named as "a recurrent deletion region" [84]. • It is associated with immune evasion [85]. • In details, it was combined with S:Y453F mutation in an immunocompromised patient that was treated with rituximab monoclonal antibodies [86]. • It might have an impact on the viral transmissibility. • S:H69- is associated with S:V70- deletion in many sequences which could cause false negative results for PCR assays that targeted spike gene such as (TaqPath assay) [83].	• S:H69- has appeared in Alpha, Eta, 21K Omicrons, 22A Omicrons and 22B Omicrons variants [83].
3	S:Y144-	NTD	• It could enable the virus to evade from immune response [63,87]. • It is appeared in a chronically infected immunocompromised patient combined with 3 amino acids deletion (141–144) [88].	• S:Y144- is present in Alpha, Eta, Mu and 21K Omicron variants [83].
4	S:W152R • S:W152L • S:W152R • S:W152C • S:W152G [89]	NTD	• It is a hotspot for substitution in which non-polar tryptophan is substituted with polar positive arginine. • It could decrease the viral binding affinity with antibodies [64]. In details, this tryptophan is a key residue in the viral pi-stacking interaction with the neutralizing antibodies and it wraps in the complementarity-determining region (CDR) loops of the antibodies' variable chains [64]. Therefore, tryptophan removal in this position could weaken the pi-stacking interaction and the created pocket of antibody's CDR loop [64].	• It combined sometimes with N501Y mutation [64]. • It was reported in SARS-CoV-2 that detected in cats in Egypt [3].
5	S:K417 • S:K417N • S:K417T	RBD	• It is associated with immune evasion [90,91]. • It could decrease the viral binding affinity with ACE2 receptor [92–94].	• S:K417N has been reported in Beta, 21K Omicron, and 21L Omicron variants [83]. • S:K417T has been reported in Gamma variant [83].
6	S:L452R	RBM	• This mutation has immune evasion effect and it could decline titer of antibody neutralization from 3 to 6 fold [64,95]. • It increase viral binding affinity to ACE2 receptor [96]. • It increase viral shedding [97] • It increase viral virulence [98] and infectivity [99].	• This mutation is reported in Delta, Kappa and Epsilon variants [83]. • It was reported in SARS-CoV-2 that detected in cats in Egypt [3].
7	S:Y453F	RDB	• It was a common mutation in mink in Denmark during the summer of 2020, thus, it may be an adaptive mutation in mink [100,101]. • It could enhance viral RBD/mink ACE2 complex binding [102]. • This mutation caused a resistance to (REGN10933) which is a mixture of antibodies [103,104].	• S:Y453F was detected with other mutations (S:H69-, S:V70-, S:M1229I and S:I692V) in immunosuppressed patient who treated with (rituximab) monoclonal antibodies [86].
8	S:S477N	RDB	• It increases RBD/ACE2 binding slightly [96]. • It causes immune evasion and a resistance to convalescent antibodies [105,106]. • It has the potential to increase viral infectivity [106]. • A combination of S:S477N, S:E484K, and S:N501Y could increase viral RBD/ACE2 binding [107].	
9	S:E484 • S:E484K • S:E484Q • S:E484A	RBD	• It causes a significant decrease in viral neutralization and cause a neutralization escape from convalescent antibodies [99,108,109]. • S:E484K may be a cause of the viral reinfection [110]. • A combination of S:E484K, S:K417N and S:N501Y could enhance, stabilize and strengthen RBD/ACE2 complex binding and reduce viral neutralization with antibodies [91]. • A combination of S:E484K, S:S477N and S:N501Y could also enhance RBD/ACE2 complex binding [91].	• S:E484K mutation is observed in Beta, Gamma, Kappa and some Alpha sequences [83].
10	S:N501 • S:N501Y (The most frequent one) • S:N501T • S:N501S	RDB	• It may affect viral binding with ACE2 receptor and antibodies recognition [83]. • S:N501Y was detected in mice [111], and S:N501T was found in mink [101] and in ferrets [112]. This suggests that it may be an adaptive mutation which contributes to the persistence of a long-term reservoir in wild rodents and mustelids [112]. • It increases viral RBD/ACE2 binding [113] as it increases the time of "open" configuration of the spike [114]. The latter ACE2 binding affinity of S:N501 mutations could be stronger in the presence of E484K and more stable with the presence of S:K417N [113]. • Additionally, S:N501Y, S:E484K , and S:S477N combined mutations also could enhance viral RBD/ACE2 binding [107] and they could reduce antibody neutralization significantly [91].	• S:N501Y mutation is observed in Alpha, Beta and Gamma variants [83]. • S:N501 mutations have also been observed in Wales, the United States, and Australia [83].

(*Continued*)

Table 4. (Continued).

	Mutations referenced to Wuhan virus	Position	Mutation effect	Notes
11	S:A570V	CTD1	• It plays a role in spike structural rearrangement as it could alter equilibrium dynamics of RBD-up open state and RBD-down closed state of spike glycoprotein [115]. This mutation has dominated the RBD-up open receptor-accessible spike form which resulted in increasing the viral RBD/ACE2 receptor binding affinity [115]. • It has immune evasion effect [64].	• A570V mutation has been reported in both Asia and North America [67]. • It was reported in SARS-CoV-2 that detected in cats in Egypt [3].
12	S:D614G	CTD2	• It increase stability of spike trimer via loop misplacement, interaction between downstream RBDs and structural rearrangements that act as a fixation tool among the spike trimer, make spike more stable, prevent its pre-maturation, improve viral assembly, enhance RDB/ACE2 binding, facilitate viral entry, increase viral infectivity and virulence [65]. • It is involved in improving viral replication in lung cells [116], increasing viral transmission, pathogenicity, evasion from host immunity [117] and decrease vaccine's effectiveness [116].	• It is the dominant mutation in all variants [65]. • This mutation was reported in SARS-CoV-2 detected in cats in Egypt [3].
13	S:H655Y	CTD2		• It was detected in Gamma variant [83].
14	S:Q677 • S:Q677H • S:Q677P	S1/S2	• It was recently detected in cat samples [3]. • It is located in the vital polybasic furin-binding region and it could enhance S1/S2 cleavage, thus, it could affect viral infectivity and pathogenicity [118].	• S:Q677H was found in 20C in the United States of America [119], Eta variants [118]. • S:Q677H was reported in SARS-CoV-2 detected in cats in Egypt [3].
15	S:P681H	Near S1/S2	• It could affect the immune recognition [120]. • It may affect immune response as it decrease the antibodies recognition [87].	• S:P681H has been reported in Alpha, Kappa and Delta [83].
16	S:A899S	FPPR	• It decrease sensitivity to monoclonal antibodies and increase the viral transmission [64,121].	• Recently, this mutation has been found in Italy [121], Saudi Arabia [122], Jordan [123] and in cats in Egypt [3].
17	S:S1051Y	S2 β-hairpin	• It could destabilize the β-hairpin structure and all the β-sheet due to breakage of hydrogen bonds between two histidine (H1048 and H1064) [3]. • It could play a critical role in viral entry, replication and could enhance viral infectivity which need further investigation [3].	• This mutation was recently observed in some cat samples in Egypt [3].

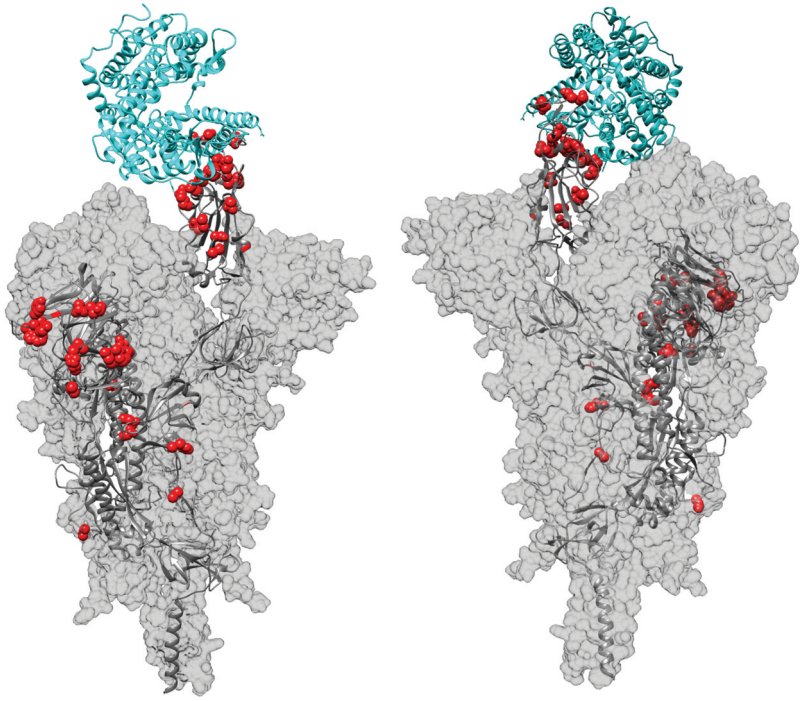

Figure 2. Spike protein mutations.

(illustrated in Figure 4) will be discussed further in sections (4.1–4.5) [147].

The figure illustrates the proposed spillover chain model in animals/human and possible mean by which

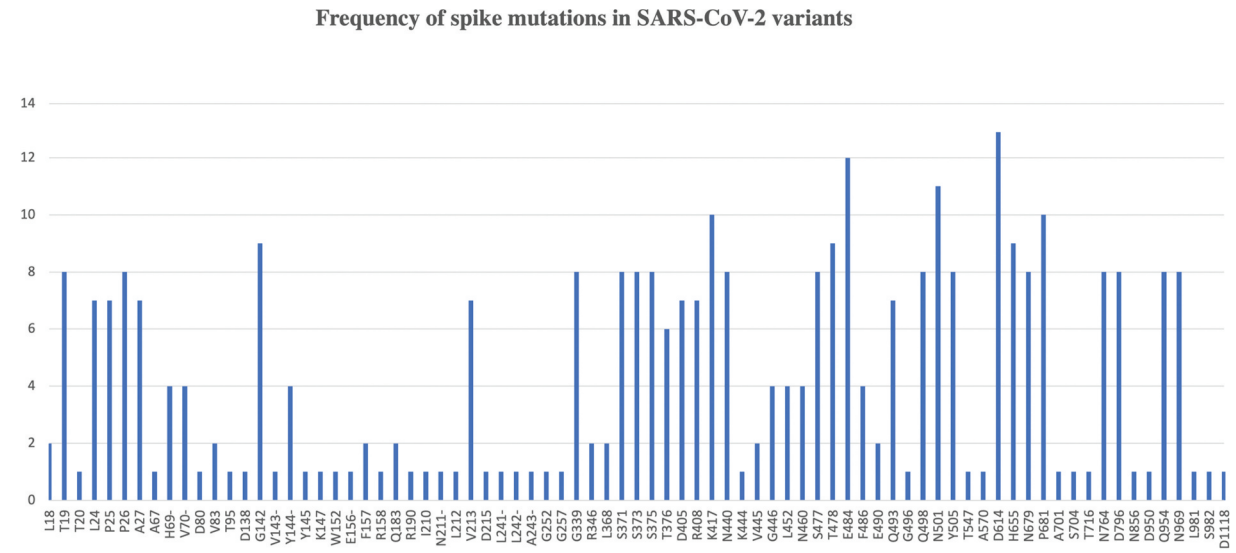

Figure 3. Frequency of the spike protein mutations in SARS-CoV-2 variants.

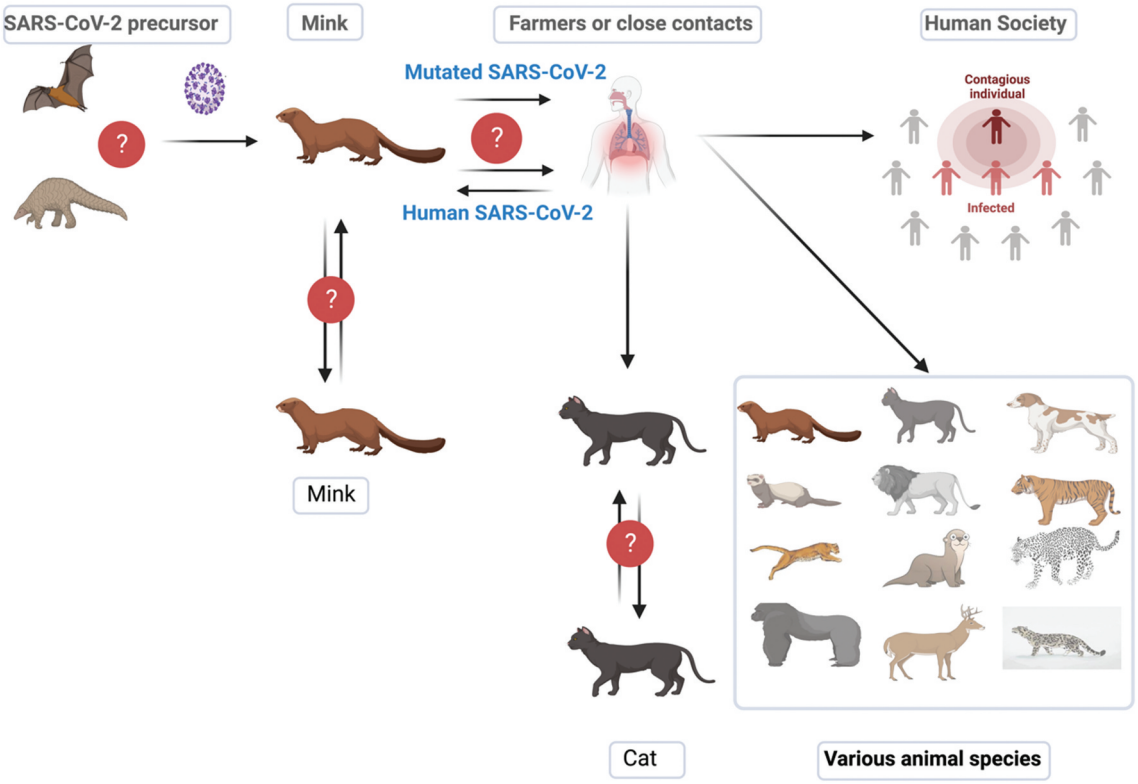

Figure 4. The proposed spillover chain of SARS-CoV-2.

such spillover may occur. The figure was generated by using Biorender website [73].

4.1. The role of bats in SARS-CoV-2 emergence and spillover chain

Even though SARS-CoV-2 outbreak was proposed to originate from bats, such proposal is yet to be verified. Moreover, the exact viral reservoir remains unknown [148]. Bats have been considered as a huge viral genomic pool as they are reservoirs for many viruses specially coronaviruses including SARS-CoV-1 and MERS-CoV [149]. Horseshoe bats (Rhinolophid bats) are proposed to be natural hosts for SARS-CoV-2 [150]. SARS-CoV-2 that was detected in human, shares a genetic similarity of (87.6%) with bat coronavirus (ZXC21/ZC45) that was detected in 2015 in China in horseshoe bats (*Rhinolophus pusillus)* [151], and a closer relationship with bat coronavirus (RaTG13) that was detected in horseshoe bats

(*Rhinolophus affinis)* in 2013 also in China with (96.2%) genetic similarity [1].

Furthermore, Egyptian fruit bats (*Rousettus aegyptiacus*) were tested for SARS-CoV-2 susceptibility and transmission within the same species [152]. Specifically, a 10^5 $TCID_{50}$ SARS-CoV-2 was intranasally inoculated into nine Egyptian fruit bats that were housed with three contact bats [152]. Consequently, 78% of inoculated bats (7/9 bats) and one of the contacts have developed rhinitis as a respiratory sign. Moreover, viral replication and shedding were detected in nasal swabs. Additionally, pathological changes and specific immune response against SARS-CoV-2 have been identified [152].

On the contrary, though the previous experiments could reveal the susceptibility of Egyptian fruit bats for SARS-CoV-2 infection, a recent study has been performed in Egypt to investigate SARS-CoV-2 natural infection in Egyptian fruit bats and their role as reservoirs, but surprisingly, all 800 tested bats were negative for SARS-CoV-2 by rRT-PCR [153]. The authors concluded that to date, there is no evidence for the contribution of Egyptian fruit bats in SARS-CoV-2 outbreak [153]. Therefore, although it was hypothesized that bats were the source of the SARS-CoV-2 outbreak, this hypothesis is yet to be confirmed.

4.2. The role of pangolins in SARS-CoV-2 emergence and spillover chain

Many inquiries have been raised about the role of pangolin as intermediate host for SARS-CoV-2 [154]. A recent study has assembled three complete genomes of pangolin coronavirus (MP789) from three Malayan pangolins, and bioinformatics analysis has displayed the genetic relationship between pangolin-CoV-2020 and SARS-CoV-2. The study have found that SARS-CoV-2 similarity is only (85.5%) with pangolin coronavirus (MP789) [1] and this relationship is not close enough to support direct emergence of SARS-CoV-2 from pangolin coronavirus (MP789) [154]. Thus, another intermediate host could be involved [154–157].

On the contrary, another study has been performed for better understanding about the role of pangolin in SARS-CoV-2 outbreak. Particularly, researchers have isolated 17 pangolin coronavirus (MP789) from 25 Malayan pangolins that displayed respiratory signs and pathological lesions [158]. Moreover, pangolin coronavirus (MP789) antibodies were detected, which had reacted with SARS-CoV-2 spike protein. In addition, comparative genetic study was performed, and the results showed that the envelope (E) of pangolin coronavirus (MP789) is the same as the envelope of SARS-CoV-2 (100%) and that the two viruses were almost identical in the membrane (M) and nucleocapsid (N) proteins with 98.6% and 97.8%, respectively. Similarity between the spike proteins of pangolin coronavirus (MP789) and SARS-CoV-2 was 90.7% and the RBD in both viruses are almost the same with only one different residue substitution in a noncritical region [158]. Therefore, this critical study has concluded two main crucial points. The first one is the possibility of pangolins to be intermediate hosts for SARS-CoV-2 because the isolated pangolin coronavirus (MP789) is genetically related to SARS-CoV-2. The second point is the possibility that SARS-CoV-2 could have resulted from a recombination event between pangolin coronavirus (MP789) and bat coronavirus RaTG13 [158].

Another supporting metagenomic study was displayed in China [159]. The latter study has identified pangolin coronavirus (MP789) in Malayan pangolins with high similarity to SARS-CoV-2 RBD [159]. This finding supported the role of pangolins as intermediate hosts for SARS-CoV-2 [159]. Additionally, another metagenomic study was carried out to detect the circulated viruses in Malayan pangolins to protect pangolins from extinction. The dominant detected viruses were pangolin coronaviruses (MP789) which cause pneumonia in pangolins and it is genetically related to SARS-CoV-2 [160]. Therefore, pangolins are likely one of the viral intermediate hosts, though the existence of other intermediate hosts is a possibility that yet to be verified.

4.3. The role of minks in SARS-CoV-2 emergence, spillover chain, reverse zoonotic and zoonotic transmission

Nevertheless many animal species are susceptible for SARS-CoV-2 infection, both reverse zoonotic and zoonotic transmission have been reported only in minks' farms [147,161]. SARS-CoV-2's clinical signs in minks varied from mild to severe respiratory signs [162].

Reverse zoonotic transmission from positive farmers to minks has been firstly reported in the Netherlands in April 2020. After that, continuous outbreaks were reported in many European and American regions [161]. Particularly, in Denmark (290 farms), the Netherlands (69 farms), Greece (23 farms), the USA (17 farms), Sweden (13 farms), Lithuania (4 farms), Canada (2 farms), as well as one farm in each of Italy, Spain, France, Poland and Latvia [162,164–166]. Furthermore, WOAH/OIE has reported 360 cases of SARS-CoV-2 infection in minks till September 2021. Specifically, 20 cases have been detected in Americas and 340 cases in Europe [166].

Indeed, SARS-CoV-2 can be transmitted among the same species in mink farms (Animal to animal transmission) [147]. On the other hand, minks also can transmit SARS-CoV-2 back to human (zoonotic transmission) [2,161] as reported in Denmark where minks could infect a farmer [147,167]. Surveillance studies suggested that the introduced SARS-CoV-2 in minks has evolved, adapted in minks and acquired new

mutations that enable its zoonotic transmission [2]. Moreover, fast spread of SARS-CoV-2 infection among mink farms has raised concerns about the effect of these mutations in minks and their impact on inter-species transmission, pathogenicity and viral re-infections [161]. These mutations include (N501T) [168,169], (Y453F), (L452M), (F486L), (G261D), and (A262S) [168]. These mutations will be discussed in detail in section 5 of this review.

4.4. The role of mouse's cellular environment in SARS-CoV-2 adaptation, and emergence omicron variant

Emergence of Omicron- SARS-CoV-2 variant was in late November 2021 in South Africa and within 2 days it was reported as a variant of concern (VOC) by World Health Organization (WHO) based on its high infection rate [170]. Omicron variant has characterized by rapid accumulation and high number of spike mutations that raise inquiries about its precursor (i.e. Animal or human origin?) [170]. The rationale behind the latter debate was the unique mutations that appeared in the Omicron variant that did not exist in previous variants; thus, researchers have proposed several theories for the evolutionary origin of Omicron variant [170]. Those theories included the long term SARS-CoV-2 adaptation in chronic COVID-19 patients (Omicron variant has human origin) [171,172] and the viral adaptation in animal host then the virus jumped back to human (Omicron variant has animal origin) [173]. Animal origin theory was based on de novo residue substitution of the SARS-CoV-2 genome that depends on host specific cellular environment that led to specific mutations [173]. For instance, Ebola virus, poliovirus, SARS-CoV-2 had displayed the same host adaptational mutations when they evolved in same hosts, whilst these viruses displayed different mutations when they evolved in different hosts [173]. Such phenomenon could have occurred, for example, due to the mutational effect of free radical species (reactive oxygen species "ROS" subset) that could oxidize nucleotides of viral genome and causing transversion (purine nucleotide "G or A" is replaced by pyrimidine nucleotide "C or T/U") [174,175] or transitions changes among purine nucleotides "G ↔ A" or among pyrimidine nucleotides "C ↔ T/U") [176,177]. Thus, the involved host with this viral adaptation could be identified via molecular analysis of the emerged mutations combined with the host specific cellular environment information [173].

Interestingly, a recent study has expected the mutational spectrum of Omicron variant before its incidence. Particularly, researchers have analysed Omicron mutations combined with human cellular environment to test if these mutations were evolved in human or not. Surprisingly, there were huge dissimilarities between human cellular environment and Omicron mutations which may suggest that the theory of Omicron-human origin can be excluded [170]. Therefore, the authors examined Omicron mutations with some non-human hosts to find the involved host where SARS-CoV-2 adapted to emerge Omicron variant by using molecular docking analysis [170]. The latter researchers found that Omicron mutations are significantly related to mice cellular environment and backbone of Omicron mutations acquired from mice. These host adaptive mutations could increase the binding affinity of viral RBD/host ACE2 receptors which enhance the viral entry [170].

Furthermore, Omicron could be an evolutionary product that resulted from recombination process between previous human and mice variants which have strengthened host-jumping possibility. Collectively, they have suggested that Omicron precursor have jumped from human to mice, then adaptive host mutations have been accumulated for around a year in mice, then it have jumped back to humans at the end of 2021 that revealed inter-species and zoonotic transmission of Omicron variant. Therefore, although emergence of Omicron-SARS-CoV-2 variant has raised many inquiries about its precursor origin in mice, such claim is very speculative and has not been proven [170].

4.5. The role of animal products and food packaging in SARS-CoV-2 emergence and spillover chain

Concerns have also been raised about the possibility of SARS-CoV-2 transmission through food and food packaging. Particularly, in March and June 2020, several meat factories in Europe and the USA reported SARS-CoV-2 outbreaks [178]. In February 2021, 95 cases were confirmed in Canada which were associated to meat plant [179]. Furthermore, other confirmed cases were documented in the USA in a meat processing factory that were claimed for many cases in the USA population [180]. Another sharp incidence in SARS-CoV-2 cases among meat plant workers was reported that indicated a common infection source [181].

Moreover, there is another concern about SARS-CoV-2 small outbreaks that had raised in some Chinese cities. The molecular analysis of these detected viruses revealed SARS-CoV-2 variant which were different from the circulated variant in China in that time frame. The previous finding evoked investigations and more research which found that the source of these small outbreaks was contaminated imported pork and raw seafood from other countries. This contamination could have occurred via the supply chains and/or packaging [182], for example, talking and breathing droplets of SARS-CoV-2 spread the infection among workers [183] and this may be the source for outbreaks.

This claim resulted from SARS-CoV-2 survival on packages without losing their infectivity up to 21 days [182]. Consequently, hygienic measures should be strictly applied for workers in food plants during processing and during food distribution [184]. Therefore, and despite the previous concerns that have been expressed regarding the possibility of SARS-CoV-2 transmission via food and food packaging, there is no evidence that SARS-CoV-2 poses a hazard to food safety and it is not considered a foodborne virus [185].

5. SARS-CoV-2 mutations could facilitate viral interspecies transmission

High mutation level among coronaviruses may indicate viral adaptation in new hosts [186]. The impact of residue substitution in the spike protein relies on changes in its hydrophobicity and polarity characteristics [168]. Consequently, significant spike mutations could enhance the viral transmission among the different species, affect viral infectivity and change the virulence of the virus [69]. Frequent amino acid mutations could have host adaptive roles [64]. Amino acids residue substitutions at RBD have the ability to alter both RBD-ACE2 binding affinity and viral immune evasion, whilst substitutions at NTD are predominantly related to the viral immune evasion [64].

The receptor binding, host susceptibility and transmission are often generally used to describe the degree and pattern of viral spread and host interaction. Indeed, virus receptor binding (or binding affinity) is not necessarily a direct indicator of the virus transmission, nor it necessarily describes the host susceptibility. However, in some cases, a correlation between the binding and transmission or host susceptibility can be found, and the changes in transmission or host susceptibility can sometimes be explained by the receptor binding.

Interestingly, an in silico study has claimed that less or unsusceptible species could become susceptible for SARS-CoV-2 infection due to RBD mutations [100]. Some researchers proposed that mouse, that was resistant to SARS-CoV-2 infection, may become susceptible for it due to RBD mutations as these mutations could enhance the binding affinity of RBD to ACE2 receptors [100]. Even though this in silico study may be useful, no claim about susceptibility of mice can be made and more experiments are needed to confirm such predictions. Another recent research suggested rapid adaptation of SARS-CoV-2 in mice after six serial passages that resulted in acquiring a single residue substitution in the RBD, after which, these mice have become susceptible to SARS-CoV-2 infection [111].

The adaptive mutations in mouse included the RBD (N501Y) (polar Asparagine → Tyrosine) substitution [82,161], which Molecular Dynamic simulations predicted that it would increase the RBD-ACE2 binding affinity [162]. The same mutation was found in B.1.1.7 strain. Using microscale thermophoresis, the purified recombinant B.1.1.7 strain RBD was found to bind 1.9 times more to the ACE2 compared to RBD originally isolated in the Wuhan strain. This was thought to make this variant highly transmissible [163]. Though indeed, transmissibility is a complex phenomenon that is an aggregate effect of many factors. Therefore, other factors such as the spike protein density, cleavage, host immunity response, and so on, may also affect transmissibility. Other reported mutations in mice were RBM (Q498H) (polar Glutamine → positively charged Histidine) and heptad repeat 1 (N969S) (polar Asparagine → polar Serine) [164].

Furthermore, RBD (N501T) (polar Asparagine → polar Threonine) mutation was detected in minks [168,169] and ferrets [112]. This mutation also has been involved in strengthening the binding affinity between RBD and ACE2 [92,101] and it could be a sign of viral adaptation in new hosts [187]. Another mutation has been detected in mink RBD, that is associated with increasing the hydrophobicity at the mutation site, is (Y453F) (Tyrosine → Phenylalanine) [188] that may contribute to the viral evolution [169] and it has increased the binding affinity between the RBD and the ACE2 4-fold more than the reference Wuhan strain, which could possibly enhance the viral transmissibility [2]. Additionally, SARS-CoV-2 detected in mink showed other mutations such as RBD (L452M) (hydrophobic leucine → hydrophobic methionine), RBD (F486L) (hydrophobic phenylalanine → hydrophobic leucine), NTD (G261D) (Glycine → negatively charged aspartic acid) and NTD (A262S) (alanine → polar serine) mutations which need further investigations to identify their impact [168].

A recent study has reported several mutations of SARS-CoV-2 that were detected in cats [3]. The latter viruses were identical to SARS-CoV-2 detected in humans during the same months and were linked to human variants that had the same amino acid substitutions. This study has strengthened the theory of SARS-CoV-2 spillover between humans and their companion animals [3]. The detected viruses in cats had seven residue substitutions in spike glycoprotein and structural modelling revealed that these residues substitutions changed the hydrophobicity and polarity of amino acids. Such substitutions may affect S1/S2 cleavage (Q677H), increase viral infectivity (D614G and S1051Y), alter binding affinity between the RBD and the ACE2 and impair critical contact areas with neutralizing antibodies (W152R, L452R, A570V and A899S) [3].

One particular example of the effect of mutation on neutralizing antibodies is the mutation in the NTD (W152R), where tryptophan was replaced

with arginine, which had weakened critical interaction points with neutralizing antibodies [64]. Therefore, Tryptophan removal in this position could weaken the pi-stacking interaction resulting in the decrease of the viral binding affinity with antibodies [64]. One the other hand, in the RBM (L452R) mutation, in which the hydrophobic Leucine is substituted with a positively charged Arginine. This mutation could decline the titre of antibody neutralization from 3 to 6 fold [95]. Furthermore, it is thought to increase viral binding affinity to the ACE2 receptor [96], viral shedding [97], viral virulence [98] and infectivity [99]. A mutation in the CTD1 (A570V) was also detected in which the non-polar Alanine is substituted with another non-polar residue Valine. This amino acid substitution is thought to result in conformational changes that affect equilibrium between up and down states of spike's RBD [115]. This mutation has led to the domination of the open RBD-up receptor-accessible spike form which resulted in increasing the viral RBD/ACE2 receptor binding affinity [115]. Therefore, the detected hydrophobic mutation (A570V) in our recent study could cause the same alteration in the conformational equilibrium [3]. A mutation in the FPPR (A899S) has also been observed in which Alanine is substituted with serine which is a polar residue. This mutation is linked to the decrease of sensitivity to monoclonal antibodies and to the increase in viral transmission [121].

Moreover, the most dominant mutation among all SARS-CoV-2 variants CTD2 (D614G) was also observed in the same study, in which the negatively charged Aspartic acid is substituted with Glycine [3]. The previous mutation was reported to enhance the viral spread by increasing the stability of the spike trimer, and at the same time slow down and reduce the spike transition to the S2 form. The flexible/disordered 630-loop in the wild strain (D614) seem to become more ordered in the G614 mutants. The more ordered loop in those mutants was found to enhance the interaction between protomers. This additional interaction seen in the structure of the mutants was proposed to be the reason for the enhanced stability of the spike trimer. Such enhanced stability was thought to increase infectivity, but at the same time, reduce the fraction of the spike that would transition from the closed form to the one RBD-up form, and subsequently reduce the S1 shedding. The reduced progression in the mutants is because an order-disorder transition in the 630-loop, in at least one of the protomers, is needed for the closed form to the one RBD-up transition to occur in the mutant, while this loop is readily unstructured (and hence can take place more rapidly) in the wild sequence. Thus, the progression of spike to the fused form is expected to be slower in the mutant, and with a higher energy barrier, compared to the wild. This explained the increased fraction of S2 observed with the wild type compared to the mutant [65]. This mutation is also involved in improving viral replication in lung cells [116], increasing viral transmission, pathogenicity, evasion from host immunity [189] and decrease in vaccine effectiveness [116].

Finally, the mutation in the S1/S2 (Q677H) was also detected in the same cat samples. That mutations involved the substitution of the polar Glutamine residue with the more positively charged Histidine [3]. This mutation is located in the vital polybasic furin-binding region and it could enhance S1/S2 cleavage, thus, is thought to affect the viral infectivity and pathogenicity [118]. Another mutation found in cat samples is in the subunit 2-β-hairpin (S1051Y) in which the polar residue (Serine) is substituted with a more hydrophobic one (Tyrosine) [3]. As a result of hydrogen bonds breakage between two histidines (H1048 and H1064), the (S1051Y) mutation could destabilize the β-hairpin [3]. Further research is required to determine whether if the later mutation affects viral entrance, replication, and infectivity [3].

6. The relationship between ACE2 receptor structure and SARS-CoV-2 host susceptibility

Recent computational modelling studies for viral RBD/ACE2 complex of different animal hosts have revealed that many mammals are susceptible for SARS-CoV-2 infection because of the partially conserved structure of the ACE2 receptor in these hosts [100,190–198]. Despite that SARS-CoV-2 could infect a wide range of mammalian species, it has low to zero incidence in birds, fish and reptiles [199]. In details, human, cat, dog, rhesus monkey and horseshoe bat that carry conserved residues (K31, Y41 and K353) in their ACE2 receptors are most likely to be SARS-CoV-2 susceptible, whilst others, which lack those amino acids, are found to be less susceptible for SARS-CoV-2 infection [193].

SARS-CoV-2 host susceptibility could be predicted by studying ACE2 receptor structure as previously mentioned [3]. In the recent study, alignment of ACE2 receptors of humans, along with other susceptible hosts (such as cats and dogs) and unsusceptible animals (such as poultry) was performed with a focus on 10 key amino acids that have polar and hydrophobic interactions with viral RBD [3]. This study revealed that chickens have 7 substitutions, dogs have 3 substitutions and cats have 2 substitutions in the latter 10 residues [3]. Changes in polarity and hydrophobicity were observed in ACE2 receptors for different animal species [3]. These substitutions probably affect the affinity of the cat/dog receptor to the human adapted virus, and hence contribute to their reduced susceptibility, though the receptor binding

affinity may not be the only factor that affects reduced susceptibility. Other factors such as host specific factors may also play a critical role.

Specifically, Q24L and M82T lead to the increase and decrease of the hydrophobicity of the corresponding regions on the binding regions, respectively. On the other hand, chickens exhibit a significant alteration in the charge distribution of the binding surface, compared to humans. Most notably, several neutral or positively charged residues (e.g. Q24E, Q42E and K31E), are substituted with negatively charged ones. Additionally, the hydrophobic residue methionine is substituted with the positively charged arginine (M82R). Such dramatic changes in the binding surface are likely to contribute to the reduced susceptibility of chickens to the COVID-19 virus circulating in humans [3]. These residue substitutions may be a contributor for SARS-CoV-2 host susceptibility as illustrated by amino acid alignment in (Figure 5). Moreover, phylogenetic analysis of the ACE2 contact surface with RBD along nearby residues were performed for different animal hosts. That analysis illustrated this critical site on the ACE2 receptors is identical in gorillas, chimpanzees and humans, whilst the percent identity between human, cats and dogs were (83.8%) and (79.5%), respectively, as displayed in Figure 6 [3].

Such observation showed the ability of SARS-CoV-2 to infect many species that could enhance the viral virulence and increase its inter-species transmission [127,200]. Additionally, it revealed that RBD recognition and binding with ACE2 cat's receptor is likely to be more favourable than that of dogs [3], which is consistent with a previous research [201]. Besides, the latter could explain the high rate of COVID disease incidence in cats than in dogs [202]. The similarity between human receptors and mink is (78.1%) which is inconsistent with the high SARS-CoV-2 infection rate (according to WOAH/OIE reports) [166]. This indicates the presence of other factors which could enhance the viral infection in minks rather than ACE2 similarity [3]. Those factors need further investigation, and they may include host factors (Age, gender, diabetes, malignancy, and chronic diseases), viral factors (viral evolution, high viral load, and high transmissibility), and environmental factors (crowding and poor ventilation). Furthermore, greater horseshoe bats and Chinese pangolins showed a similarity of 74.6% and 78.8% in the ACE2 [3], respectively, which is inconsistent with the similarity of bat CoV RaTG13

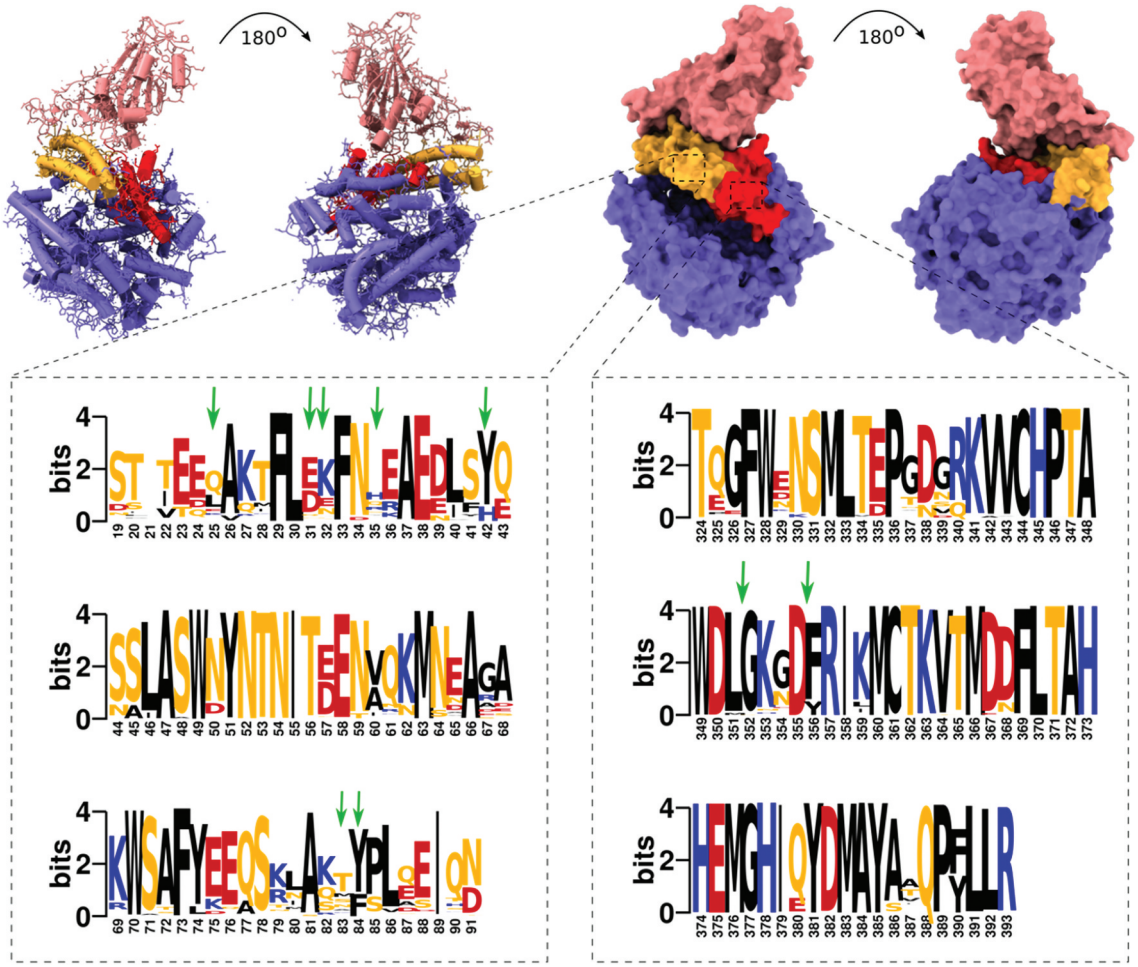

Figure 5. Sequence conservation of residues near the binding interface in host receptors (ACE2).

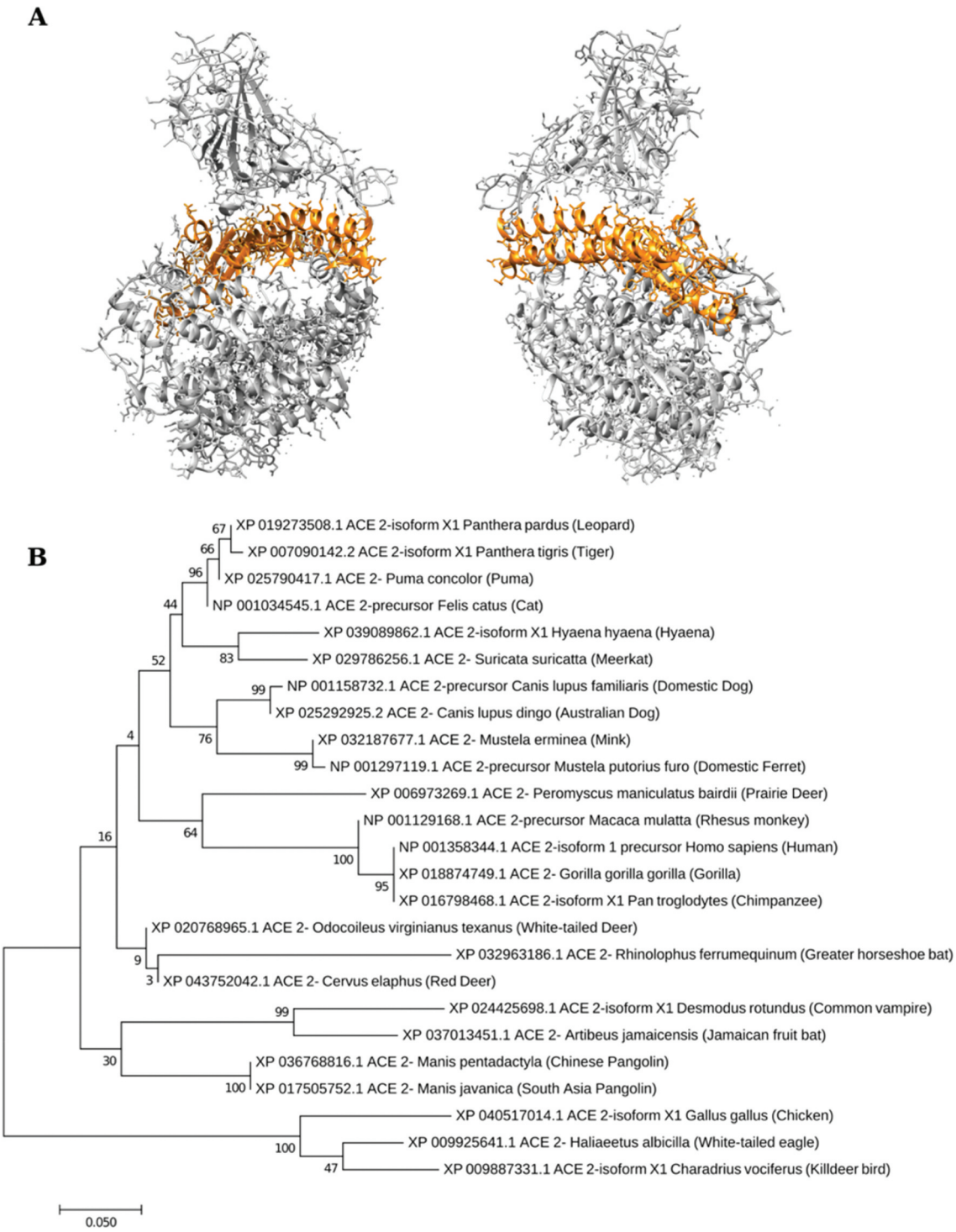

Figure 6. Phylogenetic tree of the receptor sequence from different animal species of regions at or near the binding interface with the virus RBD.

(96.3%), pangolin (MP789) (89%) with human SARS-CoV-2 isolates, suggesting that bat may be the precursor of SARS-CoV-2 [203,204], and that pangolins could be an intermediate host [205]. Therefore, these findings need further investigations to be combined together to discover other factors beside the receptor homology and ACE/RBD affinity.

To aid in visualizing alterations these mutations may have on the RBD/ACE2 interactions and understand their effect on the binding surfaces for human and various animal species, homology models along with electrostatic maps were generated for the corresponding ACE/RBD complexes [3]. Such models has revealed high similarity between human and cats receptors followed by dogs, and that there is a significant difference between human and chicken receptors with respect to polarity and hydrophobicity of the contact surface [3]. Figure 7 illustrates a comparison of the binding interfaces of predicted RBD-ACE2 complexes in six different species. The models

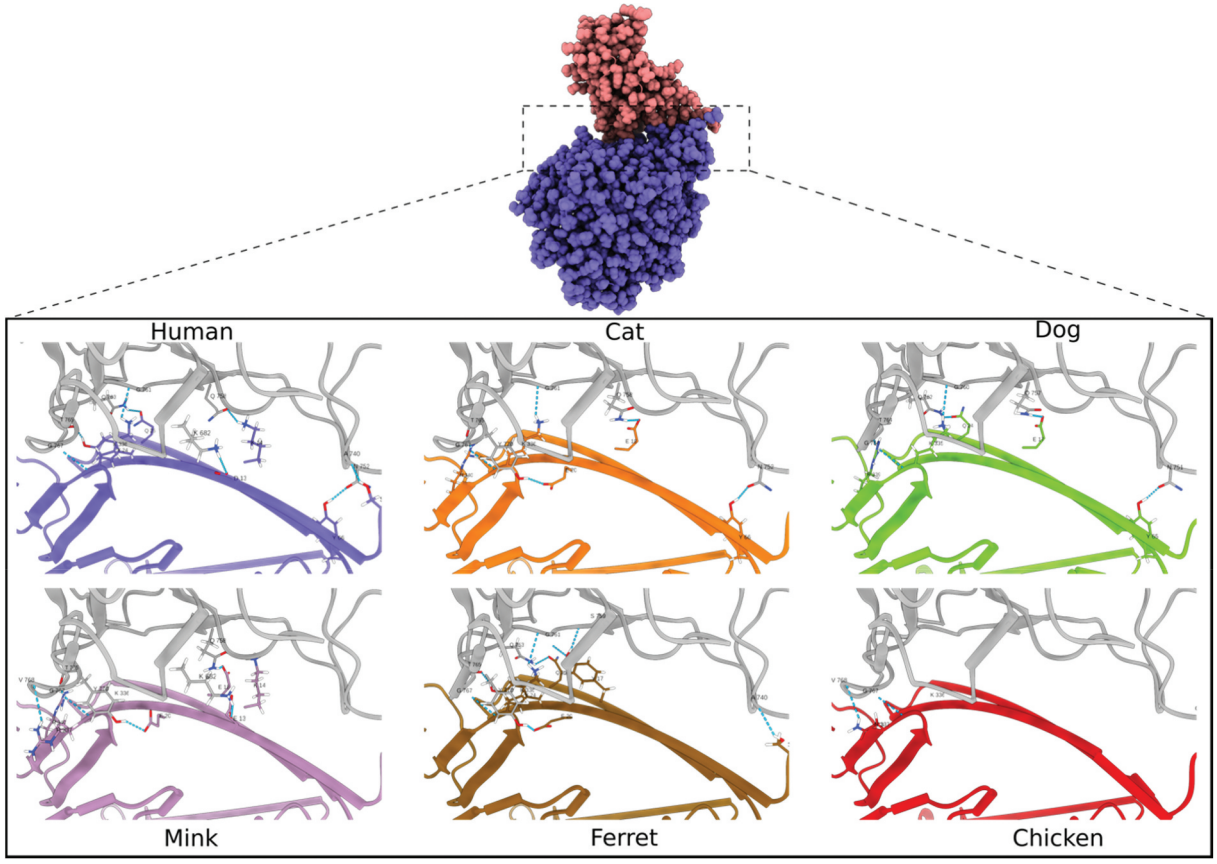

Figure 7. Comparison between binding interfaces of the viral RBD-receptor (ACE2) complexes predicted structures in different species.

support the hypothesis that polar contacts can be used as one of the predictive indicators for species susceptibility for the virus. For instance, the predicted chicken RBD-ACE2 complex lacks most of the bonds and interactions that are seen in human, cat and dog RBD-ACE2 complexes. Interestingly, the ferret and mink do have significant interactions, but are distributed differently than humans. The multiple possible patterns observed in these models suggest that a quantitative measure based on the RBD-receptor binding energetics may provide an improved predictive ability than simple qualitative sequence comparisons.

Nevertheless structural modelling could indeed facilitate prediction of host susceptibility for SARS-CoV-2 infection, the outcome of such predictions can vary greatly and does depend on the computational method used for modelling and phylogeny. In some cases, results may differ from the reality [193]. For instance, even though ferrets and mink were computationally predicted in some studies to be unsusceptible for SARS-CoV-2 infection due to the assumed weak binding of RBD/ACE2 complex, the reality was completely the opposite as both mink and ferret were proven to be highly susceptible for SARS-CoV-2 infection [169,204]. Furthermore, even though sheep is closely contact with human in farms, there is no change in the binding energy of the viral spike/ACE2 host receptor complex [193]. This means that sheep might be unsusceptible for SARS-CoV-2 infection. Therefore, although ACE2 structural analysis could provide hints on the binding affinity to viral RBD in different hosts, which in turn paves the way for making predictions about host susceptibility to SARS-CoV-2 infections [3], caution should be exercised in the methods used, and results should be validated against epidemiological data as well as experimental SARS-CoV-2 infections.

The figure illustrates logo representations of residues (with respect to the human sequence) 19–90 (shown in orange coloured cartoon and surface representations) and 324–393 (shown in red coloured cartoon and surface representations). The figure shows that these regions are highly conserved in general among many species. Residue letter codes are coloured according to polarity/charge (negatively charged residues are depicted in red, whereas positively charged and polar residues are depicted in blue and yellow, respectively). Within this region (dominated by helices) of the receptor (ACE2), residues 30–41, residues 82–84 and residues 353–357 are involved in the direct interaction. The green arrows depict residues that make critical interactions with the viral RBD. The logo illustrates that some of these residues have considerable variations between species. The degree of

variation was previously correlated with species susceptibility. The alignments used to construct these logos have been previously published in [3]. The isosurface and cartoon representations were made from DB ID 6lzg using ChimeraX [74].

Panel A shows the structure of viral RBD in complex with the PD domain of the ACE2 receptor (PDB ID 6lzg) with residues (19–90 and 324–393) depicted in orange and the remainder of the residues depicted in light grey. Panel B shows a phylogenic tree of the latter regions combined. The animal species that cluster near the human branch had been found to be more susceptible to COVID-19 infection. The figure was reproduced from [3].

The figure illustrates hydrogen bonds and polar interactions at the RBD-ACE2 contact (binding) interface for the different species predicted in homology models previously reported by Hamdy et al. [206], which were modelled based on the human crystal structure (PDB ID 6lzg). Predicted hydrogen bonds are depicted by blue dashed lines, and the viral RBD (which has similar sequences in all models) is depicted in grey. The figure was prepared by ChimeraX [74].

7. Reverse zoonosis transmissibility of SARS-CoV-2

Reverse zoonosis or anthropogenic transmission of SARS-CoV-2 has been reported as SARS-CoV-2 has the ability to jump species barriers causing cross-species transmission (Figure 4) [207]. There were outbreaks reported in many countries such as the USA, France, Spain, Denmark, Germany, Netherlands, Belgium and Hong Kong [207]. Generally, coronaviruses have virulence factors that could enhance this jumping including large RNA genomic material [127] that has mutated rapidly [159], recombination events [128], interaction with wide range of ACE2 receptors in numerous mammalian hosts [127], and viral mutations which could change its tropism, facilitate jumping species barrier [1,40] and adaptation of these viruses in new hosts [200].

Researchers investigated SARS-CoV-2 susceptibility in different animal hosts experimentally in minks, ferrets, dogs, cats, tiger, pigs, and mice [208]. Natural SARS-CoV-2 infection in animals has been emerged in thirty countries in twelve species with 584 reported cases according to the office International des Épizooties (OIE) fifth report in September 2021 [166,209]. More specifically, minks, cats, dogs recorded the highest infection incidences 360, 102 and 92 cases, respectively, followed by tigers, lions, and pumas with 12, 5 and 3 cases, respectively. Furthermore, two cases were reported in each of otters, ferrets, snow leopards, gorillas and single reported cases in white-tailed deer and Amur leopard up until September 2021 [166].

Recently, and until the end of November 2022, Coronavirus-map updates and SARS-CoV-2 records included almost 641 million human cases with around 6.6 million deaths worldwide [210]. The Office International des Épizooties (OIE) has reported (according to August 2022 report) an emergence of 692 cases of SARS-CoV-2 infection in 24 animal species in 36 countries [211]. The highest animal record was reported in the Americas followed by Europe, Asia, and Africa. In details, minks, cats, dogs recorded the highest infection scores followed by tigers, lions, and pumas. Followed by 2 cases in each of (otters, ferrets, snow leopards, gorillas, white-tailed deer, and Amur leopard). Additionally, in Europe there were recent emerged cases in Hippo and Eurasian lynx and in Asia there is a recent reported case in hamster. In the Americas, there are new species that were infected with SARS-CoV-2 including (Spotted hyena, Mule deer, Fishing cat, Binturong, Canada lynx and Coatimundi) specially in Brazil, in West Indian manatee, giant anteater and black-tailed marmoset were reported in September 2022 [212]. Events of SARS-CoV-2 reverse zoonosis in companion, zoo, and farm animals will be discussed further in sections (7.1–7.3).

7.1. *SARS-CoV-2 spillover and reverse zoonosis in companion animals (Cats, dogs and pet ferrets)*

SARS-CoV-2 has been detected in cats in some countries including Bosnia and Herzegovina [213], Italy [214], Spain [215,216], France [217], Belgium, Greece and Switzerland [218], Hong Kong (14% of examined cats were SARS-CoV-2 positive) [219] and Japan [218], the USA [202] and Brazil [218], Canada [218], the Netherlands [162] and the UK [220]. By September 2021, the WOAH/OIE had reported 102 cases of SARS-CoV-2 in cats [166].

Recently, spillover of SARS-CoV-2 from humans to their cats were reported in Egypt with a rate of 30.3% of the tested cats (10/33) by using rRT-PCR. Additionally cats have suffered from lymphocytopenia, thrombocytopenia with elevation of ferritin, C-reactive protein and D-dimers levels [221]. The latter infected cats have showed a wide range of clinical signs asymptomatic, mild and severe respiratory signs with some deaths that illustrated multiple systematic pathological lesions in lung, heart, liver intestine and kidney [221]. Another conducted study in Egypt revealed that the combination of the SARS-CoV-2 high mutation rate and cellular ACE2 homology could facilitate the viral transmission between humans and their cats [3]. Particularly, 7 amino acids were reported in SARS-

CoV-2 spike glycoprotein that were detected in cats and structural modelling has revealed that some of these mutations could affect the interaction with the neutralizing antibodies and others could influence S1/S2 cleavage, facilitate viral binding to the ACE2 host receptor and enhance viral infectivity [3].

Furthermore, anthropogenic transmission (Human origin infection) of SARS-CoV-2 was detected in four cats in Buenos Aires, Argentina in April 2021. These four cats included two females (5 years and 4 years) and two males (2 years and 13 years). These cats were closely contacted to mid-age man and wife who were COVID-19 positive. The phylogenetic analysis of SARS-CoV-2 detected in the owners and their cats revealed that the virus belonged to Alpha variant and the viruses were similar with the same mutations in owners and cats. Such finding confirm the reverse zoonotic transmission of SARS-CoV-2 from owners to cats based on case history and chronology of disease onset [222].

Besides, specific antibodies against SARS-CoV-2 which proved past viral exposure were detected in cats [204,223,224]. Some studies revealed that sensitivity of SARS-CoV-2 serology tests less than that of molecular diagnosis [69] as only 6% of tested cats were seropositive for SARS-CoV-2 in Italy [225] which provide an additional evidence for the susceptibility of cats for SARS-CoV-2 infection [202,226–228]. In contrast, another study revealed that the sensitivity of serology test was almost double that of the molecular detection. Those differences among studies could be attributed to different sampling time and experimental designs of each study [202]. Based on seropositivity rates, some studies found that cats' ability to produce antibodies against SARS-CoV-2 was lower than that of dogs [203,204,216,217,223–226,229–232]. Therefore, further research is needed to determine the ideal time of sampling for both viral RNA and antibodies to increase the reliability of the results [202].

Dogs also are susceptible for SARS-CoV-2 infection. Several cases were reported in Japan [233], Hong Kong [229] and the USA [202]. By September 2021, the WOAH/OIE had reported 92 cases of SARS-CoV-2 infections in dogs [166]. A recent study had detected spillover of SARS-CoV-2 from humans and their companion dogs in Egypt, as 24.2% of tested dogs (8/33) were positive by rRT-PCR [221]. Although some studies have reported that dogs could be infected with SARS-CoV-2 without manifesting respiratory signs [234,235], other studies have indicated that SARS-CoV-2 positive dogs varied from mild to severe respiratory symptoms [229,234,236–238]. Another recent study has documented that SARS-CoV-2 positive dogs manifest mild respiratory signs or could be asymptomatic, and interestingly, some of the infected dogs were co-infected with Parvo [221]. Clinically, some of the latter dogs have demonstrated lymphocytopenia, thrombocytopenia with elevation of ferritin, C-reactive protein and D-dimers levels [221]. Additionally, other studies have indicated that SARS-CoV-2 positive dogs varied from mild to severe respiratory symptoms [234,236–238].

Furthermore, sporadic SARS-CoV-2 cases in pet ferrets were reported in Spain and Slovenia [164,239,240]. The WOAH/OIE has reported two cases of SARS-CoV-2 infections in pet ferrets up until September 2021 [166]. Experiments have revealed that ferrets are susceptible to SARS-CoV-2 infection and are able to transmit the virus to other ferrets [161].

7.2. SARS-CoV-2 spillover and reverse zoonosis in zoo animals

Overall, by September 2021, the WOAH/OIE had reported 12, 5 and 3 cases of SARS-CoV-2 infection in tigers, lions, and pumas, respectively. Furthermore, 2 cases were reported in each of (otters, snow leopards, gorillas) and a single reported case in each of (white-tailed deer and Amur leopard) up until September 2021 [166]. After that, the WOAH/OIE reported SARS-CoV-2 infections in zoo animals including tigers, lions and pumas, otters, ferrets, snow leopards, gorillas, white-tailed deer, Amur leopard, Hippo and Eurasian lynx. By the end of April 2022, there had been reports of infections in hamster, Spotted hyena, Mule deer, Fishing cat, Binturong, Canada lynx and Coatimundi, Indian manatee, giant anteater and black-tailed marmoset, in 35 countries in Asia [212]. Furthermore, antibodies for SARS-CoV-2 were detected in 152 white-tailed deer (*Odocoileus virginianus*) in New York, Michigan, Illinois, and Pennsylvania in July 2021, suggesting the possibility of SARS-CoV-2 infection in white-tailed deer in the Midwest and Northeast USA [241].

In details, in April 2020, SARS-CoV-2 was discovered in three lions, two Amur tigers, two Malayan tigers in Bronx Zoo (New York, USA) [242]. In October 2020, another outbreak was reported in three Malayan tigers in Knoxville Zoo (Tennessee, USA). In November 2020, additional outbreaks were reported in a puma Gauteng Zoo (South Africa) and in Santiago del Estero Zoo (Argentina). In December 2020, four lions in Barcelona Zoo (Spain), three snow leopards in Louisville Zoo (Kentucky, USA). In January 2021, one lion in Tallinn Zoo (Estonia), one Bengal tiger in Wildcat Zoo (Minnesota, USA) [243], one Amur tiger and two lions in Boras Zoo (Sweden) [244,245]. In February 2021, two Sumatran tigers in Children's Zoo (Indiana, USA), two lions, one tiger and one cougar in Wild exhibit (Texas, USA) [246]. In April 2021, two lions at the Pittsburgh Zoo

(Pennsylvania, USA), three Malayan tigers at the Virginia Zoo (Virginia, USA) and eight Asiatic lions at Nehru Park (India) [234,247]. Interestingly, other important reverse zoonotic cases were reported in additional zoos in the USA including San Diego and Georgia zoos as SARS-CoV-2 was transmitted from the positive zoo staff to animals (three gorillas and four otters) [242,248].

Moreover, a research study was conducted on wild white-tailed deer (O. virginianus), and it indicated that this animal species is highly susceptible to SARS-CoV-2 infection. Multiple human SARS-CoV-2 variants, including (B.1.2, B.1.582 and B.1.596), were isolated from wild white-tailed deer. Around 35.8% of tested nasal swabs from white-tailed deer were positive for SARS-CoV-2 (129/360 samples) in Ohio, USA during the period from January to March 2021. Several residue substitutions were observed in the ORF1ab, and the spike. Those residue substitutions were uncommon in humans. The ORF1ab mutations included: Δ82–86 deletion in nsp1, T434I and P597L in nsp2, A382V in nsp12 and M474I in nsp13. The spike mutations included Δ141–144 deletion, H245Y in the NTD and E484D in RBM substitutions. Interestingly, deer-to-deer transmission was also detected [249]. Another recent study was performed on 300 white-tailed deer in Ontario, Canada during the period from November and December 2021 that involved sequencing, mutation analysis, phylogenetic, selection, and recombination analyses. The latter study detected a highly divergent variant of SARS-CoV-2 (B.1.641) in white-tailed deer. The detected variant has 76 residue substitutions (including 37 mutations related to non-human hosts). This study concluded potential evidence for SARS-CoV-2 evolution in white-tailed deer [250].

7.3. SARS-CoV-2 spillover and reverse zoonoses in farm animals

The wide use of pig-derived products in health and cosmetic sectors proposes the role of pigs in the spread and maintenance SARS-CoV-2. This certainly need further investigations [2]. Experimentally, SARS-CoV-2 could replicate poorly in cattle and pig, but cannot replicate in poultry [204,251]. Although some studies mentioned that pig is unsusceptible for SARS-CoV-2 infection [252], viral shedding and seroconversion in experimentally infected pigs indicated that 31.3% of them produced antibodies against SARS-CoV-2 and showed low level of viral shedding [253,254].

8. Animal-to-animal transmission of SARS-CoV-2

Potential animal-to-animal transmission of SARS-CoV-2 was reported when specific SARS-CoV-2 antibodies were detected in seven cats that were in the mink farms [255]. Furthermore, transmission of SARS-CoV-2 among hamsters and cats was detected [204,224]. Moreover, transmission of SARS-CoV-2 among the same species has been notified in mink farms (Animal to animal transmission).

9. Experimental infections of SARS-CoV-2

SARS-CoV-2 experimental infection of (Baboons, green monkey, rhesus monkey, crab-eating monkey) has indicated their high susceptibility for SARS-CoV-2 infection and they have showed typical signs of COVID-19 as in humans, but these signs were more severe in rhesus monkey than others [256–263].

Further experiments revealed the susceptibility of cats, hamsters, ferrets, white-tailed deer and mice for SARS-CoV-2 infection and that they could transmit the virus to other animals that were co-housed with them [112,152,203,223,224,264–268]. Additional experiments were performed in many animal species to detect the animal susceptibility of SARS-CoV-2 infections including Egyptian fruit bats, raccoon dogs, cats, white-tailed deer, rats, rabbits, mice, hamsters (Dwarf, Chinese and Syrian), cattle, Baboons, green monkey, rhesus monkey, and crab-eating monkey [207,267,269–281]. Such species displayed viral replication and shedding in respiratory tract with histopathological inflammation and specific immune responses against SARS-CoV-2 [207,271,275,282]. Moreover, experimentally infected white-tailed deer has shown evidence of vertical transmission [283].

10. SARS-CoV-2 mechanical transmission via contaminated surfaces

SARS-CoV-2 can survive in aerosols without ventilation for 3 hours [35] and it is more stable on smooth surfaces such as glass, steel, and plastic (for many days) than on rough surfaces such as paper, wood, and fabric (only for several hours) [36]. It is stable at 4°C and low pH (up to 3), but sensitive to UV radiation and it is heat labile (inactivated in 5 minutes at 70°) [36,37]. Furthermore, virus is stable up to 3 weeks in sputum, mucus, tear, saliva, blood, semen and urine of SARS-CoV-2 infected persons [284]. Additionally, the virus can be detected up to 5 weeks in some patient's stool [285] and asymptomatic carriers [286]. Thus, SARS-CoV-2 can be transmitted indirectly via contact with contaminated surfaces or other mechanical vectors, after that, the viral infection could be initiated via mucous membranes of nose, mouth, and conjunctiva [287,288].

11. SARS-CoV-2 mechanical transmission via insects and rodents

Insects and rodents could transmit many viruses between humans and animals through mechanical or biological transmission [2]. Insects have ACE2 receptors, but their structure are completely different from those in humans [289] and thus, they are unsusceptible for SARS-CoV-2 infection [2]. Furthermore, mosquitoes cannot transmit SARS-CoV-2 biologically [290–292], but house flies can transmit the virus mechanically up to 24 hours [293] via their mouth or their body from contaminated surfaces [294]. Moreover, experimentally, house flies could transmit RNA of SARS-CoV-2 to the environment up to 24 hours [293]. Furthermore, experiments revealed that some rodents such as deer mice and bushy-tailed woodrats are susceptible to SARS-CoV-2 infection [270].

In conclusion, all previous reported SARS-CoV-2 cases in animals reveal their susceptibility to SARS-CoV-2 infection and they could be a source of human's reinfection [2]. Even though, wild, zoo and domestic animals could be viral reservoirs, further studied are needed to investigate their susceptibility [295]. Therefore, the WOAH/OIE highly recommends the reporting of any incidence of SARS-CoV-2 infections in animal [166]. Furthermore, hygienic measures should be applied to people who have direct contact with animals in their occupations such as zookeepers, farmers, workers at slaughterhouses, and veterinarians to decrease the viral spread [147].

12. Conclusion

In conclusion, the present review highlights the importance of developing a universal approach to mitigate zoonotic and reverse zoonotic diseases such as COVID-19. It also sheds the light on the possible occurrence of SARS-CoV-2 spillover and reverse zoonoses from humans to their companion animals. Therefore, biosecurity measures should be applied to decrease the spread of SARS-CoV-2 among humans and animals. Furthermore, the review highlights critical residue substitutions in the spike glycoprotein of SARS-CoV-2 reported in animals As well as bioinformatics and structural modelling studies focused on potential viral evasion from immune response, increase viral infectivity and transmission. Hence, SARS-CoV-2 full genome sequencing is highly recommended to identify novel variants, monitor viral mutations and investigate impact of these mutations on viral adaptation, infectivity, pathogenicity, transmission, and the effect of these changes on therapeutics and vaccine design. Therefore, this review paves the way for in-depth studies of host susceptibility to SARS-CoV-2 infections in different animal species.

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