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Systematic Review

SARS-CoV-2 infection of domestic animals and their role in evolution and emergence of variants of concern

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ABSTRACT

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is responsible for COVID-19 pandemic, is a zoonotic RNA virus that has been reported in animals, including domestic animals. Due to the growing concern of health threat that could arise from active transmission of SARS-CoV-2 between pet owners and their pets, there is need to monitoring the emergence of a highly pathogenic strain of SARS-CoV-2 that is capable of transboundary infection, or a serious outbreak among human populations.
Methods: We carried out a search in English, on PubMed and NCBI (National Center for Biotechnology Information) SARS-CoV-2 resources for relevant journals and nucleotide sequence data, that were published between 2019 and 2023. The CoVsurver mutations application on GISAID webpage was used to analyse mutation, nucleotide sequence alignment was carried out using MAFFT (Multiple Alignment using Fast Fourier Transform) version 7 and maximum likelihood tree was constructed by bootstrapping with 1000 replicates on MEGA 11 software.
Results: A total of 47 mutations at the Spike gene region were identified, and mutation D614 was the most observed mutation. Nucleotide sequences of isolates from domestic animals had high sequence identity with Wuhan-Hu-1 reference sequence and the representative sequences of previously circulating VOCs from humans.
Conclusion: This reveals that there is spill over of previously circulating variants of concern (VOC) to household pets from their infected owners. Hence, there is an urgent need for more intense surveillance to be carried out globally to monitor evolution of SARS-CoV-2 coronaviruses as a result of human – pet association.

1. Introduction

Zoonoses (or zoonotic infections/diseases) have historically been a huge concern to public health authorities, animal health authorities, and national/global economies, due to their ability to jump from animal to human or vice-versa and cause serious illness that spreads rapidly in communities or globally, causing high morbidity/mortality, and huge economic losses [1]. Studies have shown that emergence/re-emergence of zoonoses could be as a result of urbanization, hunting/poaching, livestock farming, and live animal markets [2,3]. In addition, pet ownership has been reported to be an important avenue for zoonotic infections, and transmission of zoonotic pathogen is most often as a result of closed associations between human and domestic animals/pets (most especially cats and dogs) [3,4]. Transmission may be from human – pet or pet – human (this type is also referred to as reversed zoonoses), via inhalation, contact with contaminated fomite, ingestions, contact with body secretions, and bites or scratches of pets [5–8].

Although, parasites, bacteria, fungi, prions may cause zoonotic diseases, viral zoonoses, especially those of RNA viruses are often of greater significance to both public and animal health authorities, due to their ability to rapidly mutate into a highly transmissible and/pathogenic viral pathogen [4,9]. The high mutation rates observed among RNA viruses, including those that are involved in zoonoses, are as a result of their RNA dependent-RNA polymerase (RdRp) (main replicase transcriptase protein involved in genome replication process), which lacks proofreading mechanism, and thus, prone to error during genome replication, resulting to point mutation whereby nucleotide bases are changed, inserted, or deleted, creating new species [10–15].

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an RNA virus that is responsible for the COVID-19 pandemic is also a

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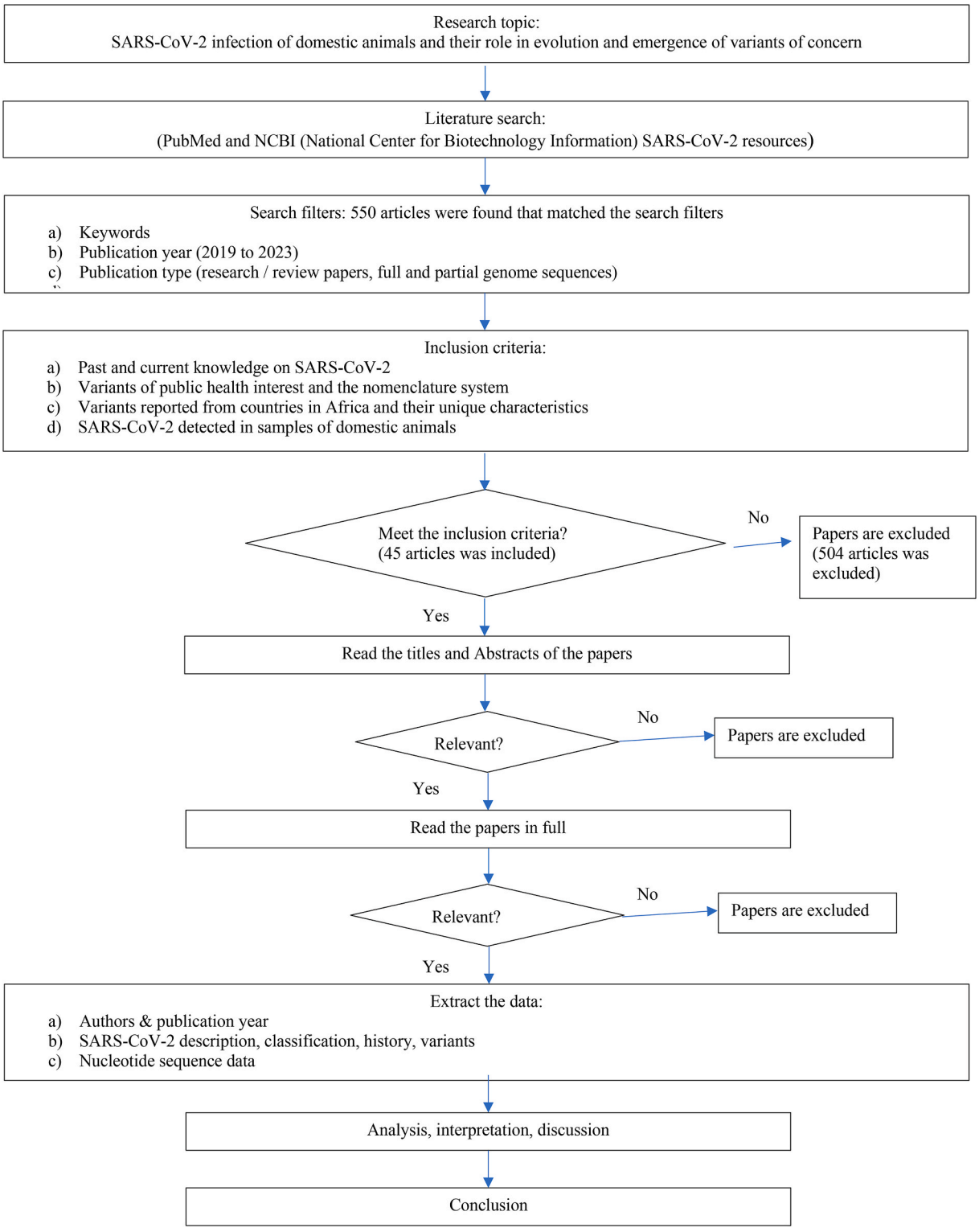

Fig. 1. Methodology of review for paper titled SARS-CoV-2 infection evolution and emergence of variants of concern.

zoonoses agent, and had been reported in animals, including domestic animals such as dogs and cat [16–19]. Since, the declaration of an end to the pandemic till the time of these review, sub lineages of the omicron variant has been circulating globally. The omicron variant is known to have enhanced transmissibility and capable of immune evasion by escaping the host's neutralising antibodies produced against existing vaccines [20]. There are many case reports of sub lineages of omicron variants detected in household pets. Studies have revealed that the peculiar characteristics of this variant are due to the numerous numbers of non-synonymous mutations, including those on the Spike (S) protein which is proven to be involved in transmissibility, disease severity, and immune escape [21]. Omicron variant poses the largest number of mutations sites of all the SARS-CoV-2 variants that has been characterised, as it has 60 substitution/deletions/insertions [22].

Although, mutations have been shown to emerge along the whole genome of the variant, more than half of the total Omicron mutations

Table 1
GISAID CoVsurver mutations application analysis of the downloaded nucleotide sequences of the SARS-CoV-2 isolates from domestic animals (dogs and cats) [1].

Source	GenBank assertion no	clade	Variant info	Country	Best reference hit	%id	Mutations
Cats	OK555092.4	GK	Rare	Thailand	Spike WIV04	99.4 %	T19R, G142D, E156G, F157del, R158del, L452R, T478K, D614G, P681R, D950N
	ON982611.1	GK	Rare	Switzerland	Spike WIV04	99.3 %	T19R, A67V, H69del, V70del, T95I, E156G, F157del, R158del, L452R, T478K, D614G, P681R, D950N
	MZ902033.1	G	Old	Spain	Spike WIV04	99.7 %	D215X, T573I, D614G, Q675del, T676del, Q677del, T678del, N679del, M1237X
	MZ496616.1	GR	Old	Peru	Spike WIV04	99.4 %	G75V, T76I, R246del, S247del, Y248del, L249del, T250del, P251del, G252del, D253N, L452Q, F490S, D614G, T859N
	MT628700.1	G	Recent	Hong Kong	Spike WIV04	99.9 %	D614G
	MW064264.1	GR	Recent	Chile	Spike WIV04	99.8 %	D614G, S1261F
	MW263337.1	GH	Recent	USA	Spike WIV04	99.8 %	T299A, D614G
Dogs	MZ914594.1	GRY	Recent	Spain	Spike WIV04	99.4 %	H69del, V70del, D138H, Y144del, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H
	MW263336.1	GR	Old	USA	Spike WIV04	99.8 %	D614G, P681H, L1224F
	ON248600.1	GK	Rare	India	Spike WIV04	99.3 %	T19R, G142D, E156G, F157del, R158del, A222V, L452R, T478K, D614G, P681R, D950N
	MT270814.1	GR	Recent	Hong Kong	Spike WIV04	99.9 %	D614G
	ON982612.1	GK	Rare	Switzerland	Spike WIV04	99.4 %	T19R, T95I, E156G, F157del, R158del, L452R, T478K, D614G, P681R
	MZ396818.2	GRY	Recent	Thailand	Spike WIV04	99.4 %	H69del, V70del, Y144del, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H

Table 2
Information on the reference sequence and representative sequences of VOC and previously circulating VOCs in humans [1].

Accession no	Variant	Country
NC_045512.2	Wuhan-Hu-1 Reference sequence	China
OK433350.1	Alpha variant (B.1.1.7)	New Zealand
OL983230.1	Beta variant (B.1.351)	USA
OL810841.1	Gamma variant (P.1)	USA
MZ828347.1	Delta variant (B.1.617.2)	USA
ON928154.1	Omicron lineage BA.2	USA

have been identified to be accumulated in the spike. The mutations identified in the spike protein of Omicron, is revealed to out-number those observed in the previous variants of concern (Alpha, Beta, Gamma, Delta), by about 3–4 times [23].

The variant possesses six substitutions (K856R, L2084I, A2710T, T3255I, P3395H, and I3758V) and two deletions of a total of four amino acids (amino acid 2083 and amino acids 3674–3676) within the ORF1a of its genome, while there are two substitutions (P314L and I1566V) in the ORF1b region. In addition, the ORF9b region is observed to have a P10S substitution and a three-residue deletion at positions 27–29 [24]. The structural proteins, have one substitution (T9I) in the envelope (E), three substitutions (D3G, Q19E, and A63T) in the membrane (M), and three substitutions and a three-residue deletion in the nucleocapsid (N) proteins, while the Spike (S) bears the highest number of mutations [25]. The S protein has 30 substitutions of A67V, T95I, Y145D, L212I, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F, three deletions of H69/V70, G142/V143/Y144 and N211, and one insertion of three amino acids (EPE) at position 214 (the changes have been described by some reports as; V143/Y144/Y145 deletion in combination with G142D and L212 deletion in combination with N211I) [25,26]. It has been shown by several studies that Omicron shares mutation such as D614G, N501Y, K417N, P681H, and the residue-substitution of E484, with previously circulating variants of concern [27].

The mutation D614G is revealed to be associated with higher viral loads at the upper respiratory tract and younger age of patients, but there is little or no information of its impact in infected domestic pets [28]. Mutation N501Y when combined with the H69/V70 deletion, and N679K and P681H mutations near the furin cleavage site, has been shown to give the Omicron variant higher transmissibility that is induced by enhanced binding between spike and angiotensin-converting enzyme 2 (ACE2), and enhanced fusion and virus infection by facilitating the cleavage of the spike into S1 and S2 [29]. The Omicron variant is also peculiar for its 15 mutations at the RBD, out of which many substitutions are located along the ACE2 receptor site [30]. This points at a likely effect on the binding function, and its capability to neutralise several antibodies that are designed to target these sites.

The previously circulating variants of concern are Alpha variant (B.1.1.7), Beta variant (B.1.351), Gamma variant (P.1), and Delta variant (B.1.617.2) [31]. These variants also emerge as a result of the accumulated mutations observed in the SARS-CoV-2 genome, most especially the mutations that occur in the spike (S) protein gene region. The S protein bears the receptor binding domain (RBD), which the virus utilises in the attachment and entry of susceptible host cells, thus, mutations that occur in this gene region has been shown to either reduce or greatly increase the transmissibility of the virus [32]. The spike (S) protein of SARS-CoV-2 determines host specificity, as it contains the receptor binding domain (RBD). Globally, numerous research has shown that mutation affecting the receptor binding domain (RBD) of the S protein, significantly affects the transmissibility, virulence and effectiveness of vaccines [33]. Thus, studying mutations in the gene coding for S protein of SARS-CoV-2 isolates from domestic pets, is key in monitoring the emergence of a highly pathogenic strain of SARS-CoV-2 that is capable of transboundary infection, or a serious outbreak among human populations.

There are concerns about the public health threat that could arise from active transmission of SARS-CoV-2 between pet owners and their pets [34]. It is also of more concern, when such infection spreads to farm animals, in the case of a pet owner that also has a farm. Although, there are no severe symptoms reported in infected animals, there is high potential of SARS-CoV-2 rapidly evolving to an agent of transboundary disease. In 2020, a study carried out by Sit et al., was the first to report SARS-CoV-2 in dogs, after this there has been several reports from

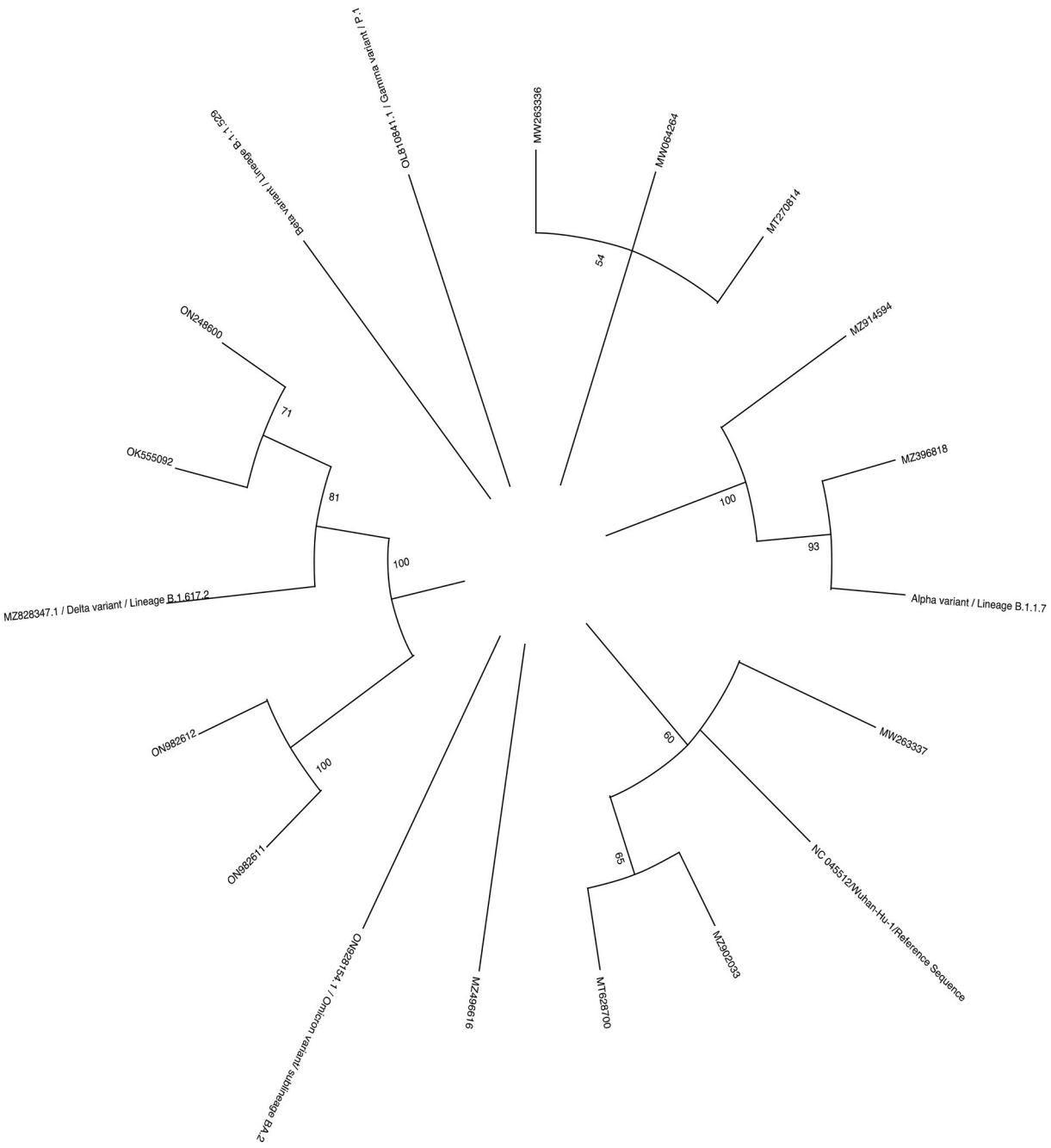

Fig. 2. Phylogenetic tree of SARS-CoV-2 isolates from cats and dogs, Wuhan-Hu-1 reference sequence, and the representative sequences of the VOC and the previously circulating VOCs from humans.

researchers in many countries, of the isolation of this pathogen in domestic animals [16]. Although, many of these reports suggest that the infection of domestic animals especially dogs and cats, is likely as a result of spill-overs from humans to these animals due to their close contacts with their owners or handlers, it is very important to also considered them as a potential intermediate host for SARS-CoV-2 transmission, and thoroughly investigate the roles they play in the evolution and emergence of new species.

In addition, the current circulating variant of SARS-CoV-2 are sub lineages of Omicron variant, which are reported to have an enhanced transmission capability [26,27,35,36]. Thus, additional mutations that occurs in an infected animal may yield a highly pathogenic strain that could cause great loss of farm animals/livestock in communities, and also rapidly spread globally. This study, therefore, identified and compared the mutations in the S gene region of some SARS-CoV-2 isolates of dogs and cats, that were submitted to the NCBI (National Center for Biotechnology Information) SARS-CoV-2 resources.

2. Methods

We carried out a search in English, on PubMed and NCBI SARS-CoV-2 resources for relevant journals and nucleotide sequence data, that were published between 2019 and 2023. For the purpose of this review, the keywords used while searching are SARS-CoV-2, zoonoses, viral zoonoses, humans, cats, dogs, reference sequence, Alpha variant, Beta variant, Gamma variant, Delta variant, Omicron variant, and respiratory swabs (Fig. 1). A total of 550 articles was initially reviewed, as they were found to contain information that was relevant to the search query and

Table 3
The identified mutations on S protein gene and their functions [1,2].

Mutations on S protein gene	Function
G75V	Unclear
T76I	Related to antigenic properties and increased infectivity
R246del	Related to Antigenic Drift.
S247del	Unclear
Y248del	Related to Antigenic Drift.
L249del	Unclear
T250del	Unclear
P251del	Unclear
G252del	Unclear
D253N	Related to antigenic drift and higher transmissibility
L452Q	Related to host change, antigenic drift, also reported to mildly increases the binding to ACE2
F490S	Related to host change, antigenic drift, and antibody escape
D614G	Related to antigenic drift, virulence, host change, increased infectivity, fast replication, fast transmission, and marginally enhanced disease outcomes.
T859N	Unclear
T19R	Related to antigenic and other properties of this strain.
G142D	Related to Antigenic Drift.
E156G	Related to Antigenic Drift.
F157del	Unclear
R158del	Related to Antigenic Drift.
L452R	Related to host change, and antigenic drift.
T478K	Related to host change, and antigenic drift.
P681R	Related to antigenic drift, virulence, increased rate of membrane fusion, internalization and thus better transmissibility, greater cytopathic effect, increased pathogenicity when in combination with D614G mutation, vaccine resistant when in combination with D614G mutation, plays a critical role in enhancing the replication in Delta variant, and enhances furin-mediated cleavage.
D950N	Unclear
A67V	Unclear
H69del	Related to antigenic drift, and when in combination with V70del it is reported to causes 2-fold higher infectivity
V70del	Related to antigenic drift.
T95I	Unclear
D215X	Unclear, but suspected to increase fusion.
T573I	Unclear
Q675del	Related to decreased infectivity.
Q677del	Unclear
T676del	Unclear
T678del	Unclear
N679del	Unclear
M1237X	Related to virulence and antigenic drift.
S1261F	Unclear
T299A	Unclear
D138H	Unclear
Y144del	Related to antigenic drift.
N501Y	Related to host change, antigenic drift, mildly increases the binding to ACE2, increased transmissibility and increased affinity for human ACE2 receptor.
A570D	Reported to stabilize the pre-fusion spike conformation.
S982A	Reported to stabilize the pre-fusion spike conformation.
D1118H	D1118H, and D215G substitutions, introduced into the D614G background, increased fusion
L1224F	Unclear
A222V	Related to antigenic drift.
P681H	Related to antigenic drift, virulence, and may increase its cleavability by furin-like proteases,
T716I	Reported to stabilize the pre-fusion spike conformation.

review objective. Also, with strong considerations for relevance, and avoidance of articles providing similar information, 46 articles was included in the study, while the remaining 504 articles were excluded.

The reports/articles used, provided information on some past and current knowledge on SARS-CoV-2, variants of public health interest and the nomenclature system, variants reported from countries in Africa, and their unique characteristics that may lead to differences in transmissibility and severity observed among individuals that reside within the continent. Literatures on detection of SARS-CoV-2 from samples of domestic animals were also included in the articles that was reviewed for this study.

The NCBI SARS-CoV-2 resources was used to search for GenBank accession numbers of SARS-CoV-2 nucleotide sequences that were already submitted by several researchers of relevant studies, and the Fasta format of 13 full genome sequences of SARS-CoV-2 isolates from domestic animals (cats and dogs) were downloaded from the GenBank [37]. In addition, the complete Wuhan-Hu-1 reference sequence, Alpha variant lineage B.1.1.7, Beta variant lineage, Gamma variant lineage P.I, Delta variant lineage B.1.617.2 and Omicron variant lineage BA.2, of isolates obtained from human respiratory swabs, were also downloaded from GenBank [37].

The CoVsurver mutations application on the GISAID webpage was used to analyse the mutations in the downloaded nucleotide sequences of the SARS-CoV-2 isolates from domestic animals [38]. The clade, variant information and the mutations identified on the Spike protein gene regions of the isolates were collated [38]. The whole genome sequences of the domestic animals, the Wuhan-Hu-1 reference sequence, and representative sequences of the SARS-CoV-2 VOC and previously circulating VOC were compiled, and the nucleotide sequence alignment was carried out using the MAFFT (Multiple Alignment using Fast Fourier Transform) version 7 [39]. The maximum likelihood phylogenetic tree was constructed by selecting the option of bootstrapping with 1000 replicates on the MEGA 11 software [40].

3. Results

About 550 relevant studies were identified and previewed before selecting the journal used in this review. We retrieved a total of 13 nucleotide sequences of SARS-CoV-2 Isolates from NCBI SARS-CoV-2 resources, out of which 7 where from cats and the remaining 8 from dogs. The Cats that served as source of isolates, were in Thailand, Switzerland, Spain, Peru, Hong Kong, Chile, and USA. While the dogs that serve as source of isolates were in Spain, USA, India, Hong Kong, Switzerland, and Thailand (Table 1). Also, from the NCBI SARS-CoV-2 resources, we retrieved 5 nucleotide sequence data of; Wuhan-Hu-1 reference sequence, and a representative sequence of each SARS-CoV-2 variant type (Alpha, Beta, Gamma, Delta, and Omicron) from human source were also obtained from NCBI SARS-CoV-2 resources (Table 2).

A total of 47 mutations at the Spike protein gene region was observed in all the downloaded nucleotide sequences of isolates from domestic animals (Table 1). The most common mutation among both the isolates from dogs and cats is D614 (Table 1). The mutations T19R, G142D, E156G, F157del, R158del, L452R, T478K, P681R, D950N, H69del, V70del, T95I, were also observed in both dogs and cats but not in a high frequency (Table 1). The mutation T716I appeared twice but was only observed in isolates from cats (Table 1). The selected sequence of the domestic animal isolates had high sequence identity (99.3–99.9 %) with the Wuhan-Hu-1 reference sequence (WIV04). The phylogenetic tree created showed the relatedness of the SARS-CoV-2 isolates from the domestic animals (cats and dogs) with the Wuhan-Hu-1 reference sequence, and the representative sequences of the VOC and the previously circulating VOCs from humans (Table 2) (Fig. 2). The functions/importance of the 46 mutations identified are revealed in Table 3.

4. Discussion

The human – pet association is a common trend that has been in existence for thousands of years ago, and cats and dogs are the most commonly seen household pets. The close association seen between this species has been implicated as the cause of several zoonotic infections, including the COVID-19 disease caused by SARS-CoV-2 virus. Sit et al. [17], in their study to determine the susceptibility of domestic pet mammals to SARS-CoV-2, carried out qPCR to detect the presence of SARS-CoV-2 RNA in specimens (deep oropharyngeal, nasal swabs and a sample of fresh faeces and/or a rectal swab) collected by veterinarians from dogs and cats in Hong Kong [17]. The report from this study reveals

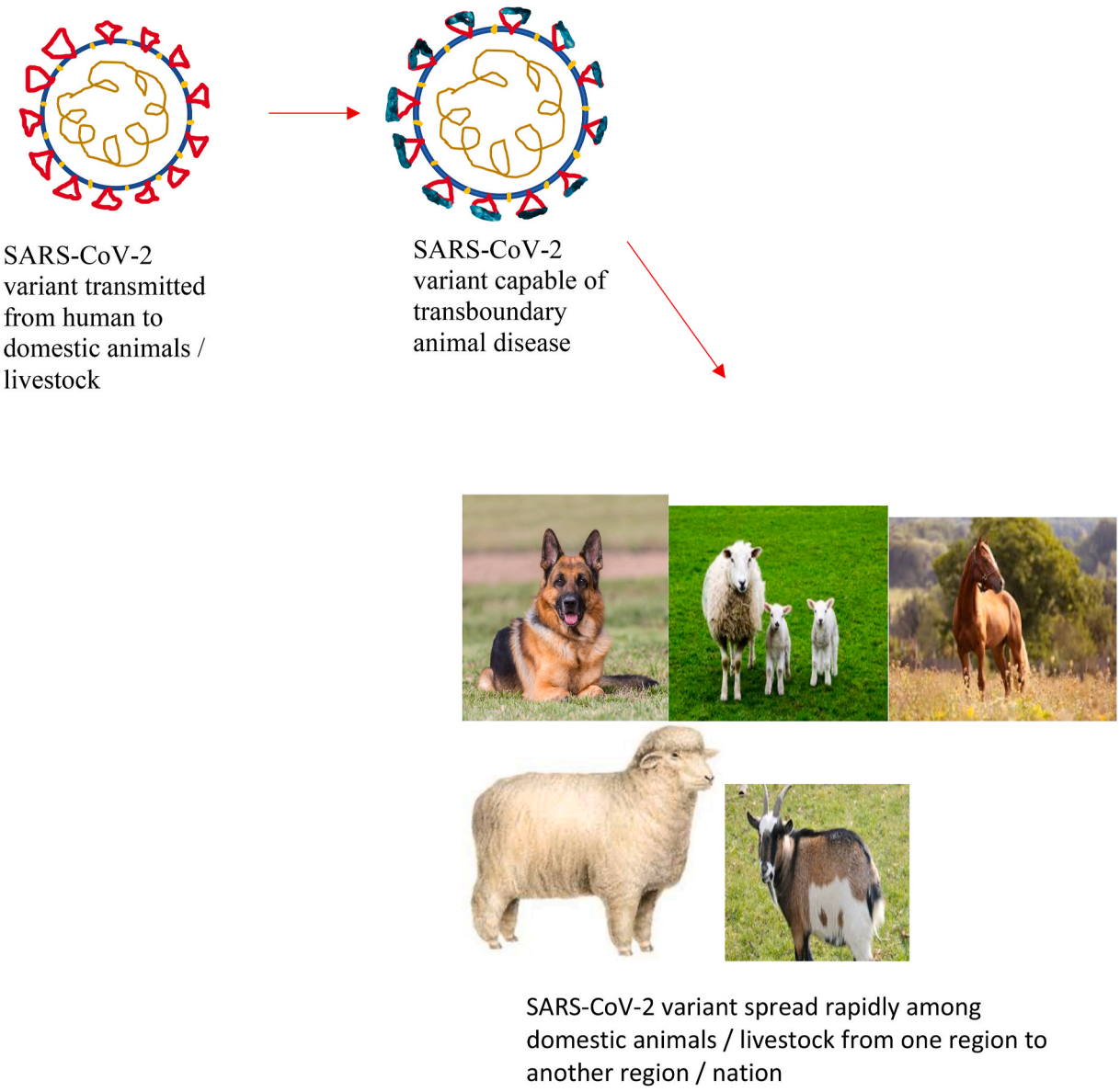

Fig. 3. SARS-CoV-2 variant transmitted from human to domestic animals evolve to variant capable of transboundary animal disease.Significance of human – pet relationship in emergence of transboundary disease.Human – domestic pet – livestock – pathogen evolves – emergence of an highly pathogenic livestock strain of SARS-CoV-2 – transboundary disease.

that dogs are susceptible to the SARS-CoV-2 viral infection [17]. Shi et al. [16], also carried out a study to determine the susceptibility of ferrets, livestock and companion animals of humans in China to SARS-CoV-2 and reported that cats have higher susceptibility to SARS-CoV-2 compared to dogs [16]. A cross sectional surveillance study carried out by Orlando et al., in Ecuador, to understand the transmission of SARS-CoV-2 from infected owners to household dogs and cats, also revealed that there is a statistically significant association between SARS-CoV-2 pet positivity and food sharing with infected owners [41]. This thereby suggests that human-to-animal transmission of SARS-CoV-2 might be actively occurring in several households, although there is need for more study to investigate and understand this transmission.

The Spike (S) protein consist of the receptor binding domain (RBD) which plays a very significant role in attachment and entry of the SARS-CoV-2 virion to the host cell, The high number of mutations (47) that was observed at the S protein gene region of all the downloaded nucleotide sequences of isolates from domestic animals, is warning of the emergence of a variant that may be capable of causing serious transboundary animal disease [14]. An article by Zhu et al. [34], shows that there is a major gap in current pandemic control and surveillance systems [34], as another study by Yen et al., revealed that a local outbreak of SARS-CoV-2 occurred in Hong Kong, due to a delta variant of concern (VOC) which had previously and persistently circulated among pet hamsters, before it later evolved and was transmitted to humans [5].

The mutation D614G was detected in all the downloaded nucleotide sequences of dogs and cats used in this study. This D614G mutation in the spike protein, which was also observed in the VOCs that were predominant during the pandemic, is implicated to be important in antigenic drift, virulence, and host change. Zhou et al. [42], revealed in their study of isogenic SARS-CoV-2 variants, that the variant with mutation D614G in their spike protein has enhanced binding to angiotensin-converting enzyme 2 (ACE2), increased replication ability, and transmissibility [42]. In another study on mutation D614G, Zhang et al. [43], reported that this mutation may increase infectivity by its ability to cause the assembly of more functional S protein into the virion [43]. Volz et al. [44], also carried out a study to evaluate the effects of

SARS-CoV-2 spike mutation D614G on transmissibility and pathogenicity and reported that the D614G mutation is associated with higher viral load [44].

Majority of the other mutations observed in this study (Table 3) were also reported by several studies to be related to antigenic drift, virulence and increased transmissibility. In addition, these mutations shows that SARS-CoV-2 infection among animals has a huge potential of being rapidly transmitted to animals in new regions and nations, thus, should be regarded as an important transboundary animal disease (Fig. 3). In a note to inventory the risks of SARS-CoV-2 contamination of pets, especially dogs and cats, by their owners, and the potential role of pets in the ongoing COVID-19 pandemic, Leroy et al. [45], reported that the high genetic recombination events that occurs in coronaviruses, including SARS-CoV-2, especially of the S protein, which is also observed in isolates of pet cats and dogs, could lead to the emergence of a new coronavirus with unpredictable phenotypic characteristics (transmissibility and virulence).

In addition, the phylogenetic tree (Fig. 2) showed some of the downloaded nucleotide sequences of isolates from domestic animals, clustered close to the representative sequences of Alpha and Delta variants from humans. This reveals that there is spill over of previously circulating variants of concern (VOC) to household pets from their infected owners. Jairak et al. [46], also corroborates this in their study where they investigated severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections in domestic dogs and cats in Bangkok and the vicinities, Thailand. Their study reveals pet animals' infection with Delta variant B.1.617.2 (a previously circulating variant of concern), and also raises awareness on spill-over of variant of concern in domestic animals due to human-animal interface [46]. Thus, there is an urgent need for continuous routine surveillance of SARS-CoV-2 in domestic pets, as the human – household pet association might be the cause of the emergence of another SARS - related CoV, that is capable of causing severe illness and loss of domestic animals and livestock, or even another pandemic.

The study was limited to the few nucleotide sequence data of SARS-CoV-2 isolates from dogs and cats, thus, a more comprehensive search and analysis of isolates from some more domestic animals and livestock will provide additional information to the significance of SARS-CoV-2 infection of both domestic animals and livestock.

5. Conclusion

The crucial need for a one-health strategy to control COVID-19 disease and other zoonotic infections cannot be undermined. Several research are focused on understanding interspecies jumping of SARS-CoV-2 by studying bat and several wild animals, but there appears to be a huge loophole in research focused on the impart of mutation of SARS-CoV-2 variants in domestic pets such as dogs and cats, and the potential of the emergence of a serious transboundary animal disease. Although, some research has emphasised on how recombination events through infection of an animal adapted CoV strain and human adapted CoV strain might produce a potentially lethal variant, that could grossly devastate domestic animals, livestock, and human population, there is still a dearth of information on this. Hence, there is an urgent need for more intense surveillance to be carried out globally in order to monitor the evolution of SARS-CoV-2 coronaviruses as a result of human – pet association.

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CRediT authorship contribution statement

Olajumoke Olufunmilayo Joseph: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Samuel Olatunde Dahunsi:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Anthony Okoh:** Writing – review & editing, Writing – original draft, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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