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Review

Global Distribution and Molecular Evolution of Bat Coronaviruses

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Simple Summary: Bats are the second most diverse group of mammals in the world, with about 1400 different species, and they play an important role in both environmental and human health. Bats have been recognized as the natural reservoirs of a large variety of viruses. Viruses that spill over from bats can cause emerging new viruses which may lead to epidemics or pandemics. In recent years, several zoonotic diseases such as Severe Acute Respiratory Coronaviruses have been linked back to bats. Some bat species serve as carriers for multiple types of pathogens without getting sick themselves due to their unique immune system adaptations. In this review, we show the global distribution and molecular evolution of bat coronaviruses to understand the risk of spill-over into other hosts.

Abstract: Bat coronaviruses cause a wide range of illnesses in humans and animals. Bats are known to harbor a wide diversity of Alphacoronaviruses and Betacoronaviruses. Betacoronaviruses have been linked to Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and other diseases such as gastroenteritis, bronchiolitis, and pneumonia. In the last 20 years, three betacoronaviruses emerged and caused widespread outbreaks in humans, including two deadly betacoronavirus epidemics, SARS-CoV, with mortality rate of 10%, and MERS-CoV, with mortality rate of 34.7%, and SARS-CoV-2, which caused the COVID-19 pandemic, with mortality rate of 3.4%. Studies have shown that bats are the main natural reservoirs for these viruses or their ancestral viruses. Observed variations in bat coronavirus genomes indicate that these viruses may have a potential to transmit to other hosts in close contact with humans and subsequently transmit to humans. As of today, there are no reported cases of direct coronavirus transmission from bats to humans. One reason for this might be that intermediate hosts are required for the transmission of bat coronaviruses to humans. Further studies are needed to map the amino acids and genomic regions responsible for the interactions between the spike of coronavirus and its receptors.

Keywords: bat; coronaviruses; molecular evolution; distribution

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1. Introduction

Bats are the second most diverse group of mammals in the world, with about 1400 different species [1]. Bats help maintain ecological balance by controlling insect populations, pollination, and seed distribution. Bats play an important role in both environmental and human health. Bats have been recognized as the natural reservoirs of a large variety of viruses [2]. Their ability to act as virus reservoirs has been associated with public health concerns [3]. In recent years, several zoonotic diseases such as Severe Acute Respiratory Coronaviruses (SARS-CoVs) have been described as bat-origin viruses [2]. Some bat species serve as carriers for multiple types of pathogens without getting sick themselves due to their unique immune system adaptations [4].

Coronaviruses (CoVs) are members of the *Coronaviridae* family in the *Nidovirales* order according to the International Committee on Taxonomy of Viruses (ICTV) [5]. They are

a large group of viruses that can cause illnesses ranging from common colds to more severe diseases and subdivided into the *Letovirinae* and *Orthocoronavirinae* subfamilies [6]. The *Orthocoronavirinae* subfamily is subdivided into four genera, *Alphacoronavirus (α-CoV)* and *Betacoronavirus (β-CoV)*, which circulate in mammals including humans, and *Gammacoronavirus (γ-CoV)* and *Delta-coronavirus (δ-CoV)*, mainly circulating in birds [2,7]. Coronaviruses have a positive-sense, single-stranded RNA genome of approximately 27–32 kb and are characterized by spike glycoprotein trimers encrusted on their envelopes, and this shape gave them the name of Coronavirus.

2. Bat Origin of Human Coronaviruses

Through next-generation sequencing technology and increased surveillance of wild animal species, a large number of novel coronaviruses have been identified. For many years, coronaviruses have crossed species barriers, causing human infections [2,8–11]. Among coronaviruses, seven CoVs have been described as infectious to humans. Two of the seven human coronaviruses (HCoVs), *HCoV-229E* and *HCoV-NL63*, belong to *alpha-CoVs*, while the other five viruses belong to *betaCoVs*, including *HCoV-HKU1*, *HCoV-OC43*, *SARS-CoV*, *Middle East Respiratory Syndrome Coronavirus (MERS-CoV)*, and *SARS-CoV-2* [8,12,13].

While *HCoV-229E*, *HCoV-OC43*, *HCoV-HKU1*, and *HCoV-NL63* usually cause mild symptoms, like common cold and/or diarrhea [14,15], the highly pathogenic viruses *SARS-CoV*, *MERS-CoV*, and *SARS-CoV-2* cause severe infections of the human lower respiratory tract, in addition to their ability to cause acute respiratory distress syndrome and extrapulmonary manifestations.

Between 2002 and 2003, an outbreak of *SARS-CoV* was reported; around 8500 people were affected and 900 died [16,17]. The mortality rate reached 9–11%, out of which 50% were individuals over 60 years of age. The first case was recorded in Hong Kong and later the virus spread to around 32 countries [18,19]. Since that time, the epidemic status of *SARS-CoV* has been controlled and the virus has not been detected in humans [20].

MERS-CoV was first detected on 13 June 2012 in a Saudi Arabian patient suffering from acute pneumonia and renal failure [21]. *MERS-CoV* is a zoonotic virus with pandemic potential. Among 2600 *MERS-CoV* human infection cases from 27 countries, 935 human-related deaths have been reported to the World Health Organization (WHO), with a case fatality rate of 36% [22]. Serological and molecular studies suggest that the main zoonotic source for *MERS-CoV* in the Arabian Peninsula is dromedary camels, but the origin of the virus is still unclear [23–25]. Human-to-human transmission was reported in clusters of *MERS-CoV* infections in South Korea, Jeddah, and Riyadh [26–28]. The identity of *MERS-CoV* sequences obtained from the patient and from the contacted camel supports the role of the camel as a reservoir for virus transmission to humans [29,30]. A retrospective serological study showed anti-MERS-CoV antibodies in archived sera collected from camels, suggesting long-term circulation of *MERS-CoV* or MERS-like CoV among camels [31].

Interestingly, phylogenetic analysis of *MERS-CoV*, *Pipistrellus* bat coronavirus *HKU5*, and *Tylonycteris* bat coronavirus *HKU4* revealed that these viruses are closely related and belong to the *Merbecovirus* subgenus, indicating that bats may be the original host for *MERS-CoV* or its ancestor [32]. Additionally, the genetic analysis of protein sequences of *MERS-CoV* and the two bat-origin coronaviruses, *HKU4* and *HKU5*, revealed that these viruses share genomic structures and have conserved polyproteins and most structural proteins but there are genetic differences in their accessory proteins and S proteins. Moreover, around 14 bat species belonging to two bat families *Vespertilionidae* and *Nycteridae*, had *MERS-CoV*-related coronaviruses, but these viruses were not the ancestors of *MERS-CoV*, as their spike proteins were basically different from that of *MERS-CoV* [33–36]. On the other hand, *NeoCoV*, *SC2013*, *HKU4*, and *HKU5* showed a high relatedness at the nucleotide level of the full-length genome with *MERS-CoV*, with similarity reaching 85.6, 75.6, 69.8, and 70%, respectively. Furthermore, *NeoCoV* shared about 95% of its amino acids with *MERS-CoV*, confirming that it could belong to the same coronavirus species as *MERS-CoV* [37]. Coronaviruses *SC2013*, *HKU4*, and *HKU5* could be classified as different coronavirus species.

Based on the phylogenetic analysis of ancestral coronaviruses, there was a hypothesis that bats were the hosts from which *MERS-CoV* transmitted to camels around 20 years ago in Africa and camels were then imported to the Arabian Peninsula [24]. Interestingly, *HKU4* virus showed high affinity to bind to bat dipeptidyl peptidase-4 (DPP4) receptor over human DPP4 receptor, unlike *MERS-CoV* [36]. Additionally, there was a hypothesis that *MERS-CoVs* had been circulating in bats and became adapted to bind to human receptor DPP4, so bat coronaviruses like *HKU4*, which have the affinity to bind to the same human receptor, might pose a great risk to human health [36,38].

In 2019, a novel outbreak caused by a new coronavirus was recorded in Wuhan City in the Hubei province of China. Infected humans showed clinical symptoms such as fever, coughing, and breathing difficulty, with progression to severe pneumonia in the most severe cases, which required ventilator support, like severely infected persons with *SARS-CoV* and *MERS-CoV* [39–41]. Later, the molecular analysis of the novel betacoronavirus was conducted and the virus was temporarily called 2019-nCoV [11,41]. In the following period, the virus was designated as *SARS-CoV-2* and was found to belong phylogenetically and taxonomically to a sister clade to the prototype bat and human *SARS-CoVs* [42].

In 1960, *HCoV-229E* was detected and caused mild common colds worldwide [43]. Interestingly, in 2008, a bat coronavirus was detected in Ghana and showed close relatedness to *HCoV-229E* with RNA-dependent RNA polymerase (RdRp) fragment, sharing 92% similarity in nucleotide sequence with *HCoV-229E*, suggesting that both viruses had the same ancestor around 200 years ago [44].

In 2004, *HCoV-NL63* was first isolated from babies suffering from pneumonia and bronchiolitis [45]. Furthermore, the prevalence of *HCoV-NL63* worldwide in hospitalized respiratory tract patients reached up to 9.3% [46]. In 2010, North American tricolored bat (*Perimyotis subflavus*) was the source for the detection of a bat coronavirus named *Appalachian Ridge CoV* in the US; this virus was closely related to *HCoV-NL63*. *Appalachian Ridge CoV* and *HCoV-NL63* are believed to have the same ancestor around 563 to 822 years ago [47,48]. On the other hand, there was a hypothesis that the origin of *HCoV-NL63* was a result of possible combination between bat coronaviruses and *HCoV-229E* [49]. In 2004, *HCoV-HKU1* was first detected in a 71-year-old male in Hong Kong; this virus is known to cause infection of the human respiratory tract [50]. After two years, in Australia, *HCoV-HKU1* was detected in samples collected from children suffering from upper or lower respiratory tract illnesses [51]. In 1967, *HCoV-OC43* was detected and was known to be responsible for 10 to 30% of the common colds occurring during the early spring or winter [52].

3. Global Distribution of Bat Coronaviruses

It has been shown that bats were reservoirs of *alphaCoVs* and *betaCoVs* in Asia, Europe, Africa, North and South America, and Australasia [49,53–65]. In recent years, there were three outbreaks caused by *SARS-CoV*, *MERS-CoV*, and *Swine Acute Diarrhea Syndrome Coronavirus (SADS-CoV)* which are related to subgenera *Sarbecovirus*, *Merbecovirus*, and *Rhinacovirus*, respectively [66–70]. Interestingly, aside from *MERS-CoV*, it was confirmed that bats were the origin of *SARS-CoV* and *SADS-CoV* [53,68,69,71,72]. Furthermore, *SARS-related CoV* and *SADS-CoV* circulate among horseshoe bats, mainly *Rhinolophus sinicus* and *Rhinolophus affinis* [53,68]; sequence identity between *SARS-related CoV* and *SADS-CoV* ranges from 96 to 98% [68]. In southeast China, related coronaviruses were detected in horseshoe bats, especially the two species *Rhinolophus sinicus* and *Rhinolophus affinis* [53,68]. This suggests that the next coronavirus outbreak can be predicted geographically by the distribution of specific bat species. On the other hand, the detection of *betaCoVs* in bats is limited by the circulation of such viruses belonging to different subgenera, including *Sarbecovirus (SARS-related CoVs)*, *Merbecovirus (Ty-BatCoV HKU4*, *Pi-BatCoV HKU5*, *Hp-BatCoV HKU25*, *MERS-related CoVs)*, *Nobecovirus (Ro-BatCoV HKU9* and *Ro-BatCoV GCCDC1)*, and *Hibecovirus (Bat Hp-betaCoV Zhejiang2013*) [7,24,73–76].

It has been suggested that the diversity of bat species and their habitats have contributed to coronavirus epidemiology. Interestingly, most *Rousettus* and *Eonycteris* bats live within the Indomalaya realm, while the Afrotropic realm is a habitat for few *Rousettus bat* species, suggesting that these ecological regions might become hotspots for the spill-over of *Nobecoviruses* among bat species. On the other hand, the co-occurrence of *SARS-like CoV* and *SADS-like CoV* in Indomalaya and Palearctic realms might have a great impact on the transmission of the CoVs from one realm to another by the help of *Rhinolophus ferrumequinum*, a *horseshoe bat* species which resides across both realms [77–84]. Additionally, *Merbecoviruses* circulate among a wide range of bats belonging to the family *Vespertilionidae*. Moreover, *Merbecoviruses* can infect variable genera of bats in the family *Vespertilionidae* in different geographical regions. Surveillance studies in bats of the *Vespertilionidae* family increased after the emergence of *MERS-CoV* and many of the *Merbecovirus* subgenus have been discovered. The genetic diversity of *Merbecoviruses* is higher than *Sarbecoviruses*, and *Nobecoviruses* and *Merbecoviruses* are more widespread in different geographical regions [24,73,75,85–87].

Bat CoVs showed a wide geographic distribution across the world caused by the diversity of bat species globally and the ability of these viruses to replicate in multiple bat species [44,81,88–93]. For instance, the same *alphaCoV (bat coronavirus HKU8)* that was previously detected in China and Hong Kong in *Miniopterus* species was also detected in *M. schreibersii* species in Bulgaria [82].

3.1. Europe

In the Netherlands, a study showed that the prevalence of CoVs in collected samples from *Myotis*, *Nyctalus*, and *Pipistrellus* bats reached 16.9% [94]. In Italy, the detection of three alphaCoVs from *Pipistrellus kuhlii* bats was reported; one of these viruses was closely related to Chinese bat CoVs [95]. Furthermore, alpha and betaCoVs were detected in different bat species in Italy, including *Pipistrellus kuhlii*, *vespertilionid*, and *rhinolophoid* bat species [96]. Other species of bats such as *Eptesicus*, *Nyctalus*, and *Hypsugo* were sources of detection of *MERS-like CoVs* in Italy [87,96,97]. Additionally, nine bat species including *Eptesicus isabellinus*, *Hypsugo savii*, and *Nyctalus lasiopterus* harbored fourteen alpha and betaCoVs in Spain [98]. In the United Kingdom, CoVs were detected with high prevalence in *Myotis natterer* bats; these bats were known to live close to humans [99]. In Germany, a study based on 315 samples from *Myotis* and *Pipistrellus* bats showed that four lineages belonging to *alphaCoVs* were detected with a prevalence of 9.8% [90], while another study analyzing 957 samples from *Myotis* and *Pipistrellus* bats showed that CoVs were detected in 1.4% of the samples [61]. In Denmark, AlphaCoVs were detected in *Myotis*, *Pipistrellus*, and *Eptesicus* bats; some of these CoVs showed close relatedness to bat coronaviruses in Germany and the UK [100]. Furthermore, out of 504 intestinal samples from *Myotis*, *Pipistrellus*, and *Miniopterus* bats in France, 12 samples were positive for alphaCoVs, with sequences closely related to bat coronaviruses detected in Germany, Luxembourg, Hungary, and Bulgaria [62]. Different studies have shown that *SARS-like CoVs* were detected by PCR in *Rhinolophus* bats in Slovenia [77], Hungary [101], Luxembourg [80], and Italy [102–104]. Moreover, in Bulgaria, samples collected from *Rhinolophus* bats were positive for *betaCoVs* [82]. In Romania and Ukraine, *betaCoVs* detected in *Pipistrellus* bats were closely related to *hCoV EMC/2012* [105]. In Croatia, the presence of SARS-CoV–2 was proved serologically in *Myotis schreibersii*, *Myotis capaccinii*, *Myotis myotis*, *and Rhinolophus ferrumequinum* [106]. In Portugal, a recent study based on 87 stool samples collected from *Pipistrellus pipistrellus* bats revealed that only one sample was positive for alphacoronavirus detected by PCR [107]. In Russia, out of 150 samples collected from different bat species, five samples were positive for coronavirus by PCR; these bat coronaviruses had high similarity with SARS-related CoVs and HCoV-OC43 [108].

3.2. North America

AlphaCoVs were detected in 50% and 17% of *Myotis occultus* and *Eptesicus fuscus* species, respectively [109]. In Colorado, a study based on more than 1000 samples collected

from 17 bat species revealed that the detection rate of alphaCoVs in fecal samples of four species reached 10%, with the majority of positive samples reported in *Eptesicus fuscus* bats [110]. In Canada, a study on 31 *vespertilionid bats* revealed that these species were infected by alphaCoVs [65]. Additionally, samples from nine frugivorous and four insectivorous bat species in Mexico were positive for alpha and betaCoVs. From these *betaCoVs*, the sequence of one virus from an insectivorous *Nyctinomops laticaudatus* bat showed high similarity with *MERS-CoV* [60].

3.3. Central and South America

In Brazil, a study conducted on more than 500 Brazilian bats of two species, *Molossus molossus* and *Tadarida brasiliensis*, revealed that from 150 pooled fecal samples, 29 were positive for alphaCoV [111]. Another study on nine different frugivorous and insectivorous species in Costa Rica, Panama, Ecuador, and Brazil revealed that alpha and betaCoV RNA were detected in 50 of more than 1500 bats, indicating the wide distribution between different bat species [112]. In Argentina, alphacoronaviruses were detected by PCR in oral and fecal samples collected from hematophagous, insectivorous, and frugivorous bats [113].

3.4. Africa

Several studies conducted in Africa showed that a large diversity of alpha and beta-CoVs was detected in different bat species [114–121]. In Kenya, detected bat CoVs were phylogenetically different from human and animal CoVs based on sequence analysis of ORFs of these viruses [122]. However, sequences of coronaviruses detected in *Triaenops* bats were shown to have high similarity with sequences of *human CoV NL63* [49]. Out of 319 bats tested for CoVs in Guinea, different alpha and betaCoVs were detected in 11% of bats [123]. In Egypt, betaCoVs were detected in desert pipistrelle bats (*Pipistrellus deserti*) and Egyptian fruit bats (*Rousettus aegyptiacus*) [117]. In Madagascar, 14 betaCoVs were detected in *Pteropus* and *Eidolon* bats [124]. Moreover, betaCoVs were detected in *Rhinolophus* and *Hipposideros* bats in Rwanda [125,126]. Alpha and betaCoVs were detected in fecal samples of insectivorous leaf-nosed bats of the genus *Hipposideros* in Ghana. BetaCoVs detected in these bats were closely related to *hCoV-229E* [44,127], suggesting that *hipposiderid* bats might be the origin host for the evolved *229E-related CoVs* in Ghana [128]. *Betacoronaviruses* belonging to subgenus *Merbecovirus* were detected in *Nycteris* bats in Ghana and showed phylogenetic relatedness to *hCoV EMC/2012* [105]. There was a close relatedness between alphaCoVs that were detected in *Hipposideros* bats from genera *Hipposideros* cf. *ruber* and *Hipposideros caffer* in Gabon and Zimbabwe, respectively [127,129]. Other studies showed that the sequences of bat CoVs detected in *Chaerophon* and *Hipposideros* bats in Kenya and Nigeria, respectively, were closely related to *SARS-like CoVs* [83,130]. Additionally, several betaCoVs detected in bats in Rwanda have been shown to cluster with *SARS-CoV* [126]. A recent study conducted in West and Central Africa showed high prevalence and genetic diversity of coronaviruses in different bat species [131]. AlphaCoVs from *Mops condylurus* bats in Nigeria was detected using deep metagenomics shotgun sequencing [132]. On the other hand, there was a hypothesis that similar to human *CoV-229E* and *SARS-CoV*, the ancestors of *MERS-CoV* may have originated from insectivorous bats belonging to the family *Vespertilionidae,* including genera *Neoromicia* and *Pipistrellus,* and this hypothesis is supported by the close relatedness between *CoV PML/2011* that was previously detected in *Neoromicia* cf. *zuluensis* bats in South Africa and *MERS-CoV* [133]. Moreover, *NeoCoV*, which was detected in the *Neoromicia capensis* bat in South Africa, in addition to *MERS-CoV,* originated from one viral species [24]. One more indicator that supports the hypothesis that bats are the evolutionary source of *MERS-CoV* is the close relatedness of the *MERS-like CoV* (strain PREDICT/PDF-2180) that was detected in a *Pipistrellus* bat in Uganda with *MERS-CoV* based on phylogenetic analysis [75]. Overall, coronaviruses of alpha and beta genera that were detected in African bats pose a great concern, as the genetic analysis of these viruses revealed that bat coronaviruses detected in these bats may be the origin of some human coronaviruses [134].

3.5. Australia

In Australia, a study based on more than 2000 bats revealed the detection of CoVs, whether by PCR or the presence of antibodies against these viruses in collected bat sera [135]. On the other hand, a serological study based on *Pteropus poliocephalus* bats in Southern Australia revealed that from 301 sera collected from these bats, 42.5% showed reactivity with *SARS-CoV* or a related virus, indicating that these bats had previously been in contact with a *SARS-CoV*-like coronavirus, while there was no reactivity with a *MERS-CoV* antigen [136]. Furthermore, in New Zealand, new lineages of alphacoronaviruses were detected in two bat species, *Mystacina tuberculate* (short-tailed bat) and *Chalinolobus tuberculatus* (long-tailed bat) [137].

3.6. Asia

In South Asia, two *Nobecovirus CoVs*, *Ro-BatCoV HKU9* and *Ro-BatCoVGCDC1*, have been found in *Rousettus leschenaultia*, a species of fruit bats [74,85,138]. Moreover, several studies showed that *Ro-BatCoV HKU9* and *Ro-BatCoV GCCDC1* have been detected in other species, *Rousettus bats* and *Eonycteris spelaea*, respectively [78,139]. A study based on more than 1000 bats belonging to more than 30 bat species in South China showed that around 89 different betaCoVs were detected by PCR in eight *vespertilionid* bat species; there were similarities between some of these viruses and *MERS-CoV* [138]. In the Tibet Autonomous Region, another study was conducted on intestinal samples collected from 21 different bat species and the results showed that 5% of the samples were positive for CoV, around 84% of the sequences were described as betaCoVs, while the remaining sequences were closely related to alphaCoVs [140]. In China, *Rhinolophus* bats were the original source for the detection of the *HKU2-related SADS-CoV* before the *SADS* outbreaks in Chinese pig farms [68,69]. In Lebanon, alpha and betaCoVs were detected in *Rhinolophus ferrumequinum* [141]. In Japan, sarbecoviruses were detected by PCR in *Rhinolophus cornutus* bats [142]. In Indonesia, Bat CoVs were detected in *Cynopterus brachyotis*, *Macroglossus minimus*, and *Rousettus amplexicaudatus* [143]. In Pakistan, out of 70 samples collected from three species of bats, including *Rousettus leschenaultia*, *Cynopterus sphinx*, and *Pteropus spp*, beta coronaviruses were detected in *Rousettus leschenaultia bats which were closely related to MERS-like CoVs* [144]. In South China, a study based on 729 rectal swabs from 20 different bat species revealed that 58 bat coronaviruses were detected by PCR in *Aselliscus stoliczkanus*, *Rhinolophus affinis*, *Rhinolophus pearsoni*, *Rhinolophus sinicus*, *Myotis chinensis*, *Myotis laniger*, *Myotis pilosus*, *Ia io*, and *Tylonycteris robustula* bat species; out of fifty-eight bat coronaviruses, twelve were related to Sarbecoviruses, seven were related to HKU6r-CoV, three were related to Decacovirus, three were related to Nyctacovirus, one were related to Minunacovirus, twenty-four were related to Rhinacovirus, and eight were related to Merbecovirus [145].

4. Molecular Evolution of Bat Coronaviruses

Most of the bat-borne viruses have been discovered through passive studies conducted during disease outbreak investigations. Advanced molecular methods, sequencing, and bioinformatics have become essential tools in studying bat-associated coronaviruses. To date, around ten thousand bat coronavirus sequences (partial and complete) have been submitted from all continents (Figure 1); bats are recognized as the major natural reservoirs of alpha and betacoronaviruses. Advances in molecular techniques have allowed scientists to identify the genome of coronaviruses and host species and to publish these in global databases [146]. Most of the submitted sequences were RdRp, whether partial or complete sequences (Figure 1B). It is remarkable that sequencing of bat coronaviruses increased after the emergence of *MERS-CoV* as a result of excessive surveillance programs for bats, as it was believed that these species are carriers of coronaviruses (Figure 1C).

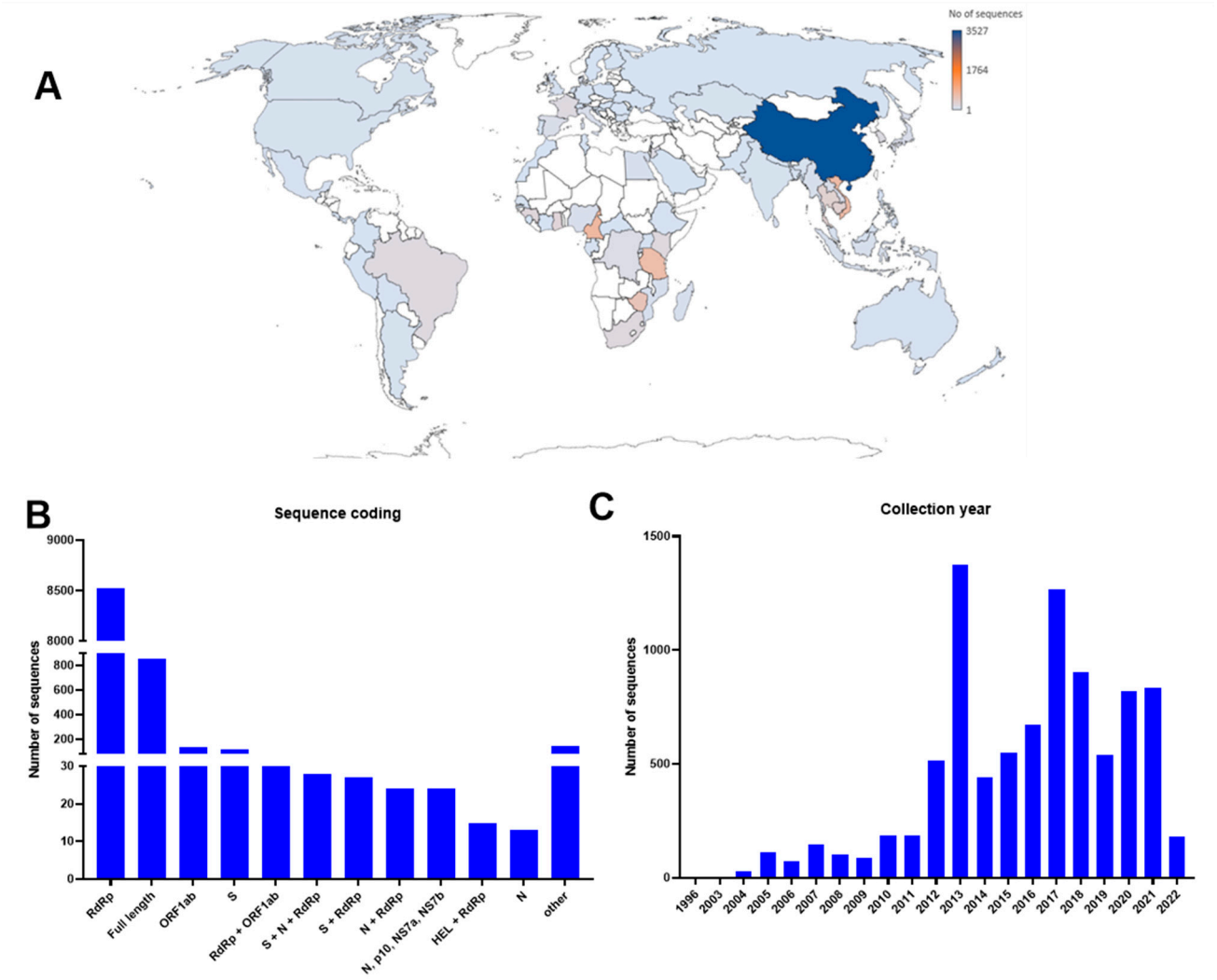

Figure 1. Geographic location of the countries which submitted coronavirus sequences to GenBank (**A**). Distribution of sequences submitted to the database by gene (**B**) and by year (**C**).

Most studies for the identification and characterization of bat coronavirus rely on the amplification and sequencing of short amplicon sequences. The limited number of complete bat coronavirus genomes can affect the classification or genetic grouping. Sequence distance is important for classification; alphacoronaviruses differ by 4.8% amino acid sequence distance in this RdRp fragment and betacoronaviruses by 5.1% amino acid sequence distance in this RdRp fragment [89,114,147]. There are several challenges in obtaining complete bat coronavirus genomes, for example, low viral RNA concentrations, limited virus isolation [148–150], availability of NGS platforms, and standard protocols for sequencing [89,114,151]. A summary of complete bat coronavirus genomes by country and virus name is provided in Supplementary Table S1.

Variations in bat coronavirus genomes were observed in alpha and betacoronaviruses and classified into subgenera (Figure 2) according to ICTV. The genome variation with evolutionary signature markers indicates that bat coronaviruses have the potential to cross the species barrier, adapt to the intermediate host, and subsequently transmit to humans, causing pandemic events in the future. As of this date, there are no reported cases of direct CoV transmission from bats to humans. This suggests that intermediate hosts are required for the transmission of CoVs to humans. The S protein of coronavirus denotes the host specificity, as it determines the usage and binding efficiency to the cell receptors. Rapid evolution of this protein is most likely driven by the viral adaptation so that the virus can

escape the new host immune system and acquire or strengthen the cell receptor binding ability [152].

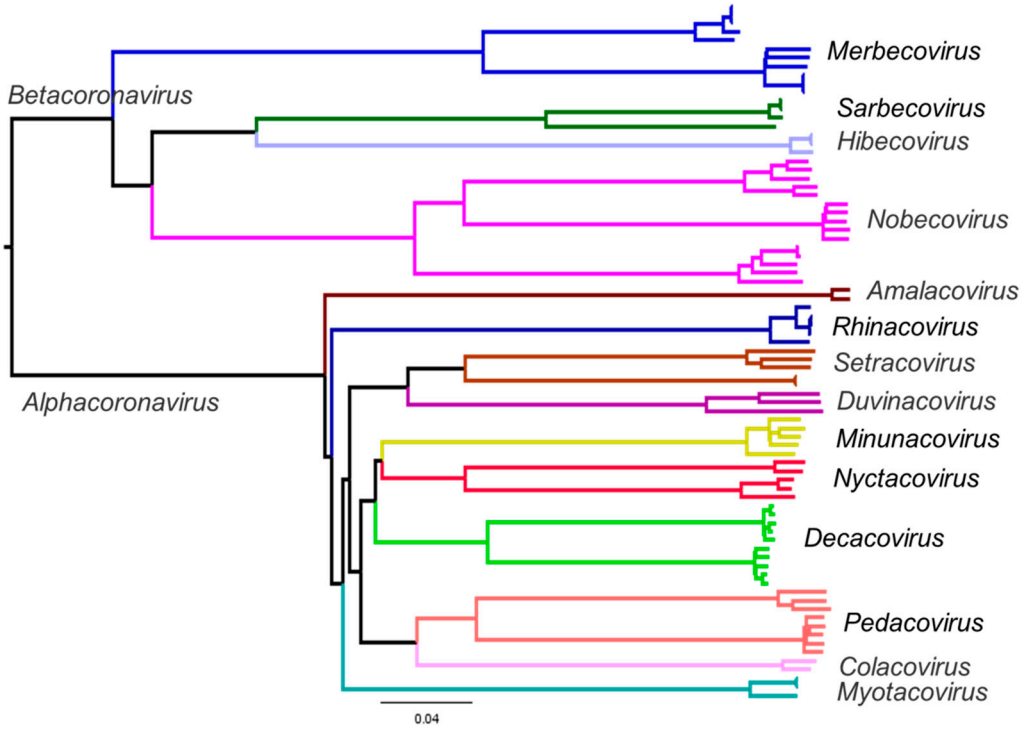

Figure 2. Phylogenetic analysis of the complete genome of alphacoronaviruses and betacoronaviruses identified from bats. Reference sequence of subgenus and similar sequences were retrieved from GenBank and aligned using MAFFT (v.7), and neighbor-joining method trees were calculated with substitution model Jukes-Cantor using MAFFT (v.7). Trees were visualized using FigTree version 1.4.2 (http://tree.bio.ed.ac.uk/software/figtree/, accessed on 11 June 2023). Subgenera of alphacoronaviruses include 10 subgenera (Colacovirus, Decacovirus, Duvinacovirus, Minuacovirus, Myotacovirus, Nyctacovirus, Pedacovirus, Rhinacovirus and Setracovirus); betacoronaviruses include 4 subgenera (Hibecovirus, Merbecovirus, Sarbecovirus and Nobecovirus) able to infect bats.

A single aspartic acid-to-glycine change at position 614 in the S protein has been identified to increase replication of *SARS-CoV-2* in humans [153,154]. Previous studies showed that the deletion of an amino acid at site 7, in addition to the substitution of five amino acids in the spike protein of *SARS-CoV*, are critical for the S protein-ACE2 interaction [155,156]. Therefore, the mutations in RBD (or domain B) within the spike protein S1 subunit are critical for the recognition of host receptors. Human coronaviruses *HCoV-NL63* bind angiotensin-converting enzyme 2 (ACE2), *HCoV-229E* viruses bind alanine aminopeptidase (APN), and *HCoV-OC43* and *HCoV-HKU1* bovine coronaviruses bind N-acetyl-9-O-acetylneuraminic acid [157,158]. *SARS-CoV* and *SARS-CoV-2* were similar to coronaviruses *HCoV-NL63*, while *MERS-CoV* binds to DPP4 [159]. Recent study showed that TMPRSS2 is a functional receptor for *HKU1* due to specific conserved amino acids in the *HKU1* receptor binding domain [160]. Further studies are needed to map the amino acids and regions responsible for the interactions between the spike of the coronavirus and its receptors based on the variability of binding affinity of different coronaviruses with a wide range of different receptors and subsequently different hosts.

5. Conclusions and Future Directions

Alpha and betaCoVs are common and diverse in bats. This is shown by the detection of such viruses on almost all continents in various insectivorous and fruit bats. This review highlighted the fact that bats are plausibly the natural reservoir of coronaviruses

of importance to public and animal health. This evidence will likely be stronger as more genomic data on bat CoVs become available. It is also clear that bat CoVs are genotypically and phenotypically diverse and acquire mutations over time that enable them to adapt to new reservoirs and hosts. However, most of the studies on the ecology of bat CoVs rely on small cross-sectional surveillance studies that are certainly not providing the complete picture of the diversity and distribution of bat CoVs globally. Hence, it is important to emphasize that more surveillance for bat CoVs and other bat viruses is important. Generated data from said projects will aid in assessing potential human, animal, and environmental health risks associated with those detected viruses.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/zoonoticdis4020014/s1, Table S1: Summary of complete bat coronavirus genomes by country and virus name.

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