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Review
Infectious Disease

Characterization of bat coronaviruses: a latent global threat

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ABSTRACT

It has been speculated that bats serve as reservoirs of a huge variety of emerging coronaviruses (CoVs) that have been responsible for severe havoc in human health systems as well as negatively affecting human economic and social systems. A prime example is the currently active severe acute respiratory syndrome (SARS)-CoV2, which presumably originated from bats, demonstrating that the risk of a new outbreak of bat coronavirus is always latent. Therefore, an in-depth investigation to better comprehend bat CoVs has become an important issue within the international community, a group that aims to attenuate the consequences of future outbreaks. In this review, we present a concise introduction to CoVs found in bats and discuss their distribution in Southeast Asia. We also discuss the unique adaptation features in bats that confer the ability to be a potential coronavirus reservoir. In addition, we review the bat coronavirus-linked diseases that have emerged in the last two decades. Finally, we propose key factors helpful in the prediction of a novel coronavirus outbreak and present the most recent methods used to forecast an evolving outbreak.

Keywords: Bats; coronaviruses; SARS-CoV2; immune response; dissemination

IMPLICATIONS

This review contributes a concise introduction to coronaviruses isolated from bats and discusses their distribution in Southeast Asia. We also discuss the unique adaptation features in bats that confer the ability to act as a potential coronavirus reservoir. In addition, we review the bat coronavirus-linked diseases that have emerged in the last two decades. Finally, we propose key factors helpful in predicting a novel coronavirus outbreak and present the most recent methods used to forecast an evolving outbreak (**Fig. 1**).

INTRODUCTION

Coronaviruses (CoVs) are members of the *Coronaviridae* family in the *Nidovirales* order. They are characterized by spike glycoprotein trimers encrusted on the virus's envelope, resembling a crown; therefore, they were named coronavirus [1]. The coronavirus genome is a positive-sense, single-strand RNA molecule with an approximate 27–32 kb size [2]. Among the class

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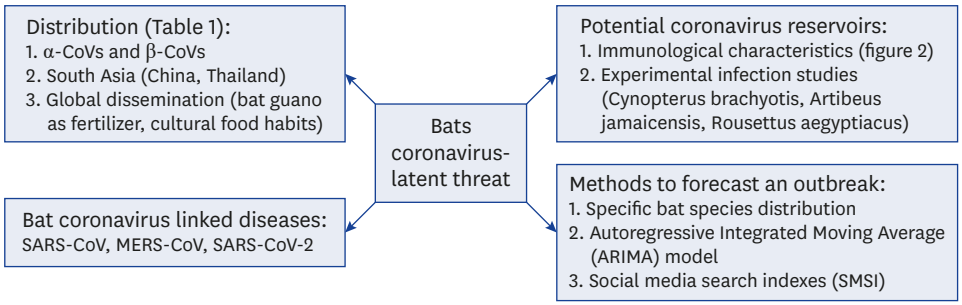

Fig. 1. Schematic summary illustrating the characterization of bat coronaviruses.
CoV, coronavirus; SARS, severe acute respiratory syndrome; MERS, Middle Eastern respiratory syndrome.

of +RNA viruses, CoVs possess the largest RNA molecule among mammalian viruses [3]. The *Coronavirinae* subfamily consists of four genera: (α-) *Alphacoronavirus*, (β-) *Betacoronavirus*, (δ-) *Gammacoronavirus* and (γ-) *Deltacoronavirus* [4], of which α-CoVs and β-CoVs infect bats and other mammals. In contrast, δ-CoVs and γ-CoVs cause diseases in birds [5].

Two-thirds of the coronavirus genome is constituted by two overlapping open reading frames: ORF1a and ORF1b, which encode the viral polymerase (RdRp) and nonstructural proteins implicated in the viral replication–transcription machinery [6]. The leftover fraction of the genome codes for four structural proteins (spike protein [S]; envelope protein [E]; membrane glycoprotein [M]; and nucleocapsid protein [N]), the order of which is conserved in all CoVs [7]. It is noteworthy to mention that the ORF1a, ORF1b, and the four structural proteins are almost invariable; thus, variations in the length of the coronavirus genome are determined by the number and size of accessory proteins [8]. The exceptional functionality of the coronavirus accessory genes is due to their co-evolution with their natural hosts; therefore, identification and elucidation of the roles that the accessory proteins have in their natural and spill-over hosts are essential [9].

Expansion of viral genetic material through recombination and gene insertion is a frequent phenomenon in CoVs and allows the acquisition of accessory protein-encoding genes, thereby enhancing the possibility of adaptation and infection in new hosts [10]. To date, nine subgenera of α-CoVs: *Colacovirus*, *Decacovirus*, *Duvinacovirus*, *Minunacovirus*, *Myotacovirus*, *Nyctacovirus*, *Pedacovirus*, *Rhinacovirus,* and *Setracovirus*; and four subgenera from β-CoVs: *Sarbecovirus*, *Merbecovirus*, *Nobecovirus,* and *Hibecovirus* have been detected in bats [11].

Bats are a key natural reservoir of both α-CoVs and β-CoVs [5]. Moreover, an increase in the number of coronavirus species will persist as there are numerous unclassified CoVs [12].

Over the past year, reviews concerning bats and CoVs and the role of bats as infectious disease reservoirs were published, particularly as the topic related to the current pandemic. For example, Chathappady et al. focused on the occurrences of viral diseases, including SARS and Middle East Respiratory Syndrome (MERS). The Calistri et al. report discussed human activities and viral spill-over from bats to humans [13]. do Vale et al. [14] commented on an animal origin of SARS-CoV-2 and its possible hosts/reservoirs and reviewed all natural animal infections and experimental evidence using animal models. Sharma et al. [15] focused on coronavirus evolution and SARS-CoV-2-related modes of transmission, detection techniques, and current control and prevention strategies. Irving et al. [16] concentrated on the mechanisms that underpin host defense systems, the immune tolerance of bats, and the ramifications for

human health and disease. Andersen et al. [17] described the origin of SARS-CoV-2 based on a comparative analysis of genomic data, the notable features of the SARS-CoV-2 genome, and the scenarios by which they could have arisen. However, the unique adaptation features of bats, the key factors required to predict a novel coronavirus outbreak, and the most recent methods helpful in forecasting outbreak evolution remain unclear.

In this review, we present a concise introduction to CoVs found in bats and discuss the unique adaptation features of bats that confer the ability to act as potential coronavirus reservoirs. In addition, we review bat coronavirus-linked diseases, suggest key factors helpful in predicting a novel coronavirus outbreak, and discuss the most recent methods for forecasting outbreak evolution.

SOUTHERN ASIA DISTRIBUTION AND GLOBAL DISSEMINATION OF BAT CORONAVIRUSES

The only animals among the Class Mammalia capable of flying are bats, which provides an exceptional migratory advantage compared to terrestrial mammals. Furthermore, bats are the second most numerous order among the mammalian orders and have an extensive distribution in all the continents except *Antarctica* (**Table 1**). According to phylogenetic analysis, *Chiroptera* can be classified into two suborders. On one side, the *Yinpterochiroptera* is comprised of one *Pteropodidae* (megabat) and five *Rhinolophoidea* (microbat) families; on the other hand, the *Yangochiroptera* consists of thirteen microbat families [18].

Geographical localization of coronavirus outbreaks related to bats can be estimated from the regional distribution of their habitats. Even though α-CoVs and β-CoVs have been identified in bat colonies in Africa, the Americas, Australasia, Asia, and Europe [19-25], it seems that α-CoVs are more extensively disseminated at the global level as their detection rate is higher [26].

The Southeast Asia region is considered a hotspot for novel infectious outbreaks [27]. The region's prominent economic development and demographic growth have had adverse effects on the biosphere and its biodiversity [28]. China is the third-largest country by area and the most populated nation in the world. Its extensive area has a highly diverse climate and harbors an enormous diversity of bats and bat-borne viruses. For this reason, it is not surprising that the majority of CoVs have been isolated in China [29]. A study conducted on 35 species of bats in 15 provinces of China has shed light on coronavirus infections in bats. Coronavirus infection was frequently observed in bat colonies in those provinces; however, most CoVs appear to have a high degree of host restriction within the bat populations. For instance, CoVs in infected *Myotis ricketti* from Anhui, Guangdong, and Yunnan provinces are similar despite the distances between the regions, a phenomenon that might be attributed to bat migration. Encountering CoVs specific to a particular bat genus in a different location but with a similar environment suggests that viral dissemination occurs along with host dispersion [30]. On the other hand, different bat species inhabiting the same location have presented distinct CoVs [31].

To the southeast of China, where a wide diversity of horseshoe bats live, there have been SARS-CoV and SADS-CoV outbreaks. Both CoVs were detected principally in *Rhinolophus sinicus* and *Rhinolophus affinis* [32,33].

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Table 1. Recent coronaviruses detected in bats

Taxonomic level			Sampling			Intermediate host	New host	New name	Characteristics
CoV genus	CoV subgenus	CoV species	Time	Location	Bat host				
Alphacoronavirus	Decacovirus	BatCoV-HKU10	2012; 2005–2010	Chakan, Thailand; Hong Kong and Guangdong province, China.	*Rhinolophus shameli* [19]; Rousettus leschenaultia [75]	-	*Hipposideros pomona* (Pomona leaf-nosed bats)	Hi-BatCoV HKU10	· Interspecies transmission. · Rapid adaptation in the new host by changing its S protein [75].
	Minunacovirus	CoV1A/B	2008, 2012	Chakan, Thailand	*Hipposideros lekaguli* [19]	-	-	-	· The G+C content of CoV1A/B is 38.2 and 38.6%, respectively. · ORFs 1 (ORF1a and ORF1b) represent around 70% of the genomes [76].
	Rhinacovirus	BatCov-HKU2	2013–2016	Guangdong province, China	*Rhinolophus spp.*	-	*Sus scrofa domesticus* (Pigs)	SADS-CoV	· Genome identity of SADS-CoV and HKU2-CoV is 95%. · SADS-CoV-infected pigs show watery diarrhea, intestinal lesions, and rapid weight loss [33].
	Duvinacovirus	229E-like viruses	2007–2010	Kenya	*Hipposideros* sp.	Camelids [11]	*Homo sapiens* (Human)	Human coronavirus NL63 (HCoV-NL63)	· HCoV-NL63 origin took place through zoonotic recombination.
	Setracovirus	NL63-like viruses			*Triaenops afer*				· A large part of the HCoV-NL63 genome comes from NL63-like viruses circulating in *Triaenops afer*; interestingly, the spike protein gene has its origin from a 229E-like virus circulating in *Hipposideros* bats [20].
	Unclassified	BatCoV-HKU6	2006	Hong Kong	*Myotis ricketti* [75]	-	-	-	-
Betacoronavirus	Merbecovirus	Bat derived MERS-like CoV	2012–2013	Bisha, Saudi Arabia	*Taphozous perforatus*	*Camelus dromedarius* (Dromedary camel)	*Homo sapiens* (Human)	MERS	· Possible relocation of MERS-CoV ancestors from Africa to the Arabian Peninsula [77-79]
	Sarbecovirus	Bat derived SARS-like CoV	2011–2012	Yunnan Province, China	*Rhinolophus sp.* [60]	*Paguma larvata* (Palm civet)	*Homo sapiens* (Human)	SARS-CoV	· Molecular clock analysis has shown that bat and civet virus strains are closely related to SARS-CoV. · Divergence took place a few years before the outbreak [32]. · The similarity of the full-length spike (S) glycoprotein in palm civet SARS coronavirus and SARS-CoV isolated from humans is 98.0% [79].
		-	-	-	-	-	*Homo sapiens* (Human)	SARS-CoV-2 [80]	-

CoV, coronavirus; SADS, Swine acute diarrheaoea syndrome; MERS, Middle Eastern respiratory syndrome; SARS, severe acute respiratory syndrome.

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Thailand is another country notable for its diversity in bats, with 139 different species reported to date. However, only 25 of these species have been examined for coronavirus infection. Thus far, the results have revealed that coronavirus infection in bats is a common phenomenon in Eastern Thailand, affecting several species of bats. Both α- and β-CoVs have been detected among members belonging to *Hipposideridae* family in Eastern Thailand. Moreover, bats have been shown to host SARS-related CoVs over a prolonged period, thus becoming a potential source of viral infections in other species [19,34].

Interestingly, bat species belonging to different families but inhabiting the same cave have been shown to harbor the same bat coronavirus species. For example, *Hipposideros lekaguli*, was reported to harbor a *Miniopterus* coronavirus in clade1 and *Rhinolophus shameli* in clade 5 [19]. This demonstrates the versatility and adaptability of CoVs to infect bats at the inter- and intraspecies levels.

In five Thai provinces near Cambodia a large number of coronavirus detections have been reported in recent years [12]. The distribution of bats and bat-borne CoVs is closely related to anthropogenic activities. Both *Scotophilus* and *Myotis* easily adapt to human-made environmental changes and inhabit anthropogenic habitats. Nevertheless, there is a latent risk associated with the αCoV_1 and αCoV_2 sub-clusters detected in *Scotophilus* and *Myotis*, respectively [35].

Furthermore, humans have taken advantage of bat guano for use as a fertilizer in Southeast Asian countries. In Cambodia, for instance, *Scotophilus* is reared in farms where their bat guano is subsequently collected [36], despite the risk associated with this activity due to the previous detection of β-CoVs in Thai bat guano farms [35]. Bats are adapting to new environments derived from human actions, accentuating the risks related to natural landscape changes and the risk of novel viral outbreaks. Additionally, the speed of deforestation in Southeast Asia is the fastest among global tropical regions, with a loss of 1.2% of the forested area annually; thereby, fragmenting the natural environment and forcing bats to live nearer to humans [37].

Finally, cultural and food habits are crucial factors in the exposure and dissemination of viral infections from bats. Southeast Asian countries are well known for their wet markets where it is possible to find live-slaughtered animals as they are believed to be more nutritious or possess healing properties. These practices and assumptions may promote viral transmission in such populations [29,30].

BATS AS POTENTIAL CORONAVIRUS RESERVOIRS: IMMUNOLOGICAL CHARACTERISTICS

Bats have been considered optimal reservoir hosts of CoVs thanks to their species diversity, the varied habitats they inhabit, and their long-distance migration abilities [31]. As reservoirs, bats may harbor viruses that are potentially pathogenic to humans. To elucidate how bats can harbor zoonotic viruses more effectively than other mammals, epidemiologists have assessed bat immune responses to viral infections by implementing *in vitro* research studies. Papenfuss *et al*. have been pioneers in sequencing the transcriptome from *Pteropus alecto* immune tissues. From the approximately 18,600 known genes, nearly 500 genes (3.5% of the bat genome) were associated with the immune system. Subsequently, similar studies were performed in *Artibeus jamaicensis* and *Rousettus aegyptiacus*, in which approximately 1.86%

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and 2.75% of the genome were associated with immune system-related genes, respectively [38,39]. These genes play a central role in T-lymphocyte activation, cytokine production, and expression of pattern recognition receptors (PRRs) such as toll-like receptors (TLRs), nucleotide oligomerization domain-like receptors (NLRs), and retinoic acid-inducible gene-I (RIG-1)-like receptors (RLRs) [39,40].

Once a viral infection has successfully occurred in a cell, signaling cascades that bring about the expression of pro-inflammatory and antiviral cytokines are activated. For instance, interferons (IFN), which are antiviral cytokines, trigger the expression of IFN-stimulated genes (ISGs) that suppress virus replication by disrupting the virus life cycle at any point (entry, uncoating, genome replication, particle assembly, egress) [41]. The necessity of identifying the PRRs in bat cells that may be involved in antiviral signaling after an RNA viral infection is a key factor related to the importance of bats as reservoirs of CoVs.

In all animals, TLRs have been conserved throughout evolution. In mammals, for example, these receptors deal with the recognition of particular products derived from microbial metabolism [42]. Human cells sense viral RNAs via TLR3, TLR7, and TLR8 [43]. Although TLR1-TLR10, which are homologous to those in humans, have been sequenced in *P. alecto*, their function remains unknown in bats [44]. Likewise, RIG-I and melanoma differentiation-associated gene 5 (MDA5), which in human cells are in charge of detecting exogenous RNA, have been identified in several bat genomes through transcriptome analysis [40,45]. In *P. alecto*, RIG-I and MDA5 show similarities in their primary structures and tissue expressions to their human homologs [46].

Though many genes essential to responses to viral infections are present in bat genomes, analog comparisons of the way they function in the immune responses of human and bat cells is a research field yet to be explored [9].

Once pathogen-associated molecular patterns (PAMPs) have been detected by PRRs, they give a signal to express antiviral and pro-inflammatory cytokines through the help of adaptor proteins. Proper regulation of inflammatory responses is imperative to reduce tissue damage. For this, bats are endowed with mechanisms that limit pro-inflammatory responses without compromising type I IFN responses to limit virus propagation [46]. For instance, c-Rel, a NF-κB family member, acts as a repressor of tumor necrosis factor (TNF) and, in *Eptesicus fuscus*, dictates the inflammatory threshold by decreasing the level of TNF [45]. Diminished NLRP3, an important inflammasome sensor, induces a weak inflammatory response in bat immune cells affected by a viral infection [47]. Both the natural capacity of bats to regulate high and risky levels of inflammation [48,49] and their ability to host a great diversity of viruses may be the reason behind their long life span and capability to avoid clinical diseases.

The expression of IFNs is induced via the transcription factors interferon regulatory factor 3 (IRF3) and IRF7 [49,50]. In MERS-CoV-infected *E. fuscus* cells, IRF3 drives antiviral signaling. A failure or knock-down of IRF3 diminishes IFNβ induction; thus, a weak response to viral infection [51]. Moreover, IRF7 mRNA is constitutively and extensively expressed in *P. alecto* cell tissues compared to that in human cells, eliciting a quicker response to viral infections in bats [52]. To sum up, among mammals, bats have an exceptional and efficient response to RNA virus infections, the result of suppressing virus replication suppression via IFN induction while curbing an excessive pro-inflammatory response, which can be potentially harmful to tissues (**Fig. 2**).

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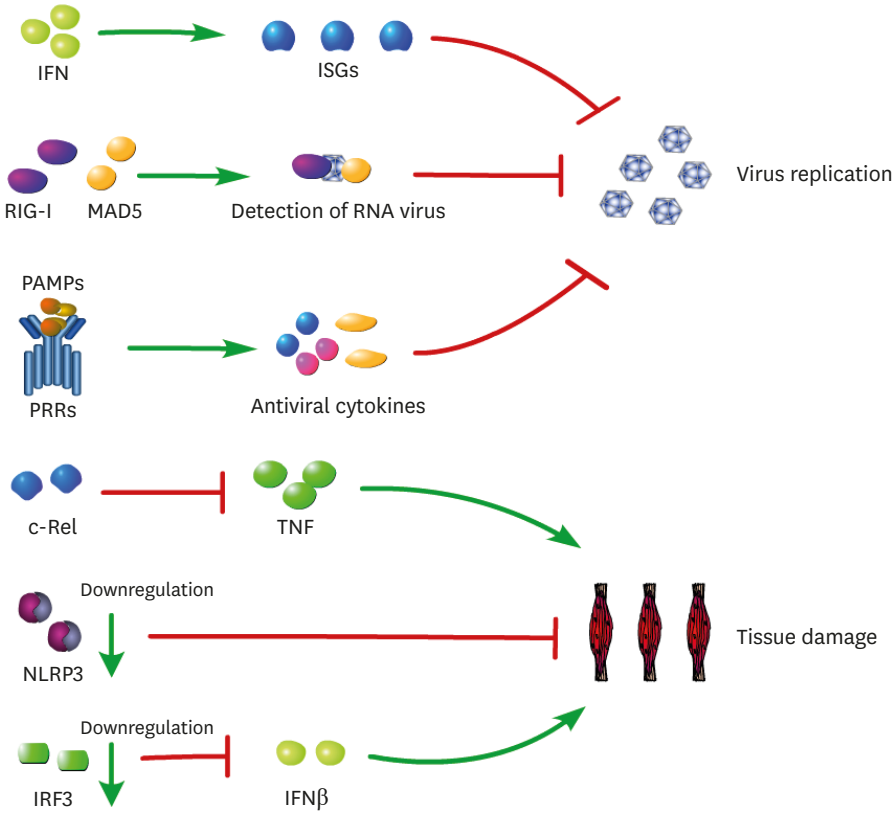

Fig. 2. Schematic diagram of immunological characteristics in bats after coronavirus infection. Among mammals, bats have an exceptionally efficient response to RNA virus infections accomplished by suppressing virus replication while curbing an excessive pro-inflammatory response, which can be potentially harmful to tissues. IFN, interferon; ISGs, IFN-stimulated genes; RIG-I, inducible gene-I; MDA5, melanoma differentiation-associated gene 5; PAMPs, pathogen-associated molecular patterns; PRRs, pattern recognition receptors; TNF, tumor necrosis factor; NLRP3, NLR family pyrin domain containing 3 IRF3, interferon regulatory factor 3.

BATS AS POTENTIAL CORONAVIRUS RESERVOIRS: EXPERIMENTAL INFECTION STUDIES

To better understand the physiological relevance of bat immune responses, *in vivo* studies have been tested, though there is still a need for further experiments. An initial study reported by Watanabe *et al.* aimed to isolate a bat coronavirus. In that study, they observed through reverse transcription–PCR testing that 57.1% of insectivorous bats and 55.6% of frugivorous bats were infected with CoVs; nevertheless, *in vitro* culture of the viruses was unsuccessful. In an attempt to propagate CoVs, viruses detected in *Cynopterus brachyotis* intestinal samples were orally administered to *Rousettus leschenaulti* specimens. As expected, 2–5 days after infection, virus replication was detected by quantitative real-time PCR (qPCR), but interestingly, no pathogenic effect was reported. This pioneering study confirmed that a coronavirus could be easily transmitted across species; furthermore, bat species selection is relevant when studying bat CoVs *in vivo* [53].

A second study carried out by Munster *et al.* had the objective of elucidating the origin of MERS-CoV. For this, Jamaican fruit bats (*Artibeus jamaicensis*) were infected with MERS-CoV/EMC2012. The authors reported viral infection in the bats respiratory and intestinal tracks; however, once again, no clinical symptoms of disease such as inflammation were detected.

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The observations of that study supported the hypothesis that bats may be the ancestral reservoirs of MERS-CoV [54]. Since this study, MERS-like viruses have been reported in bats; however, virus isolation and *in vitro* culture remain unsuccessful [55,56].

The latest study on this subject was conducted following the outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In that study, *Rousettus aegyptiacus* specimens were intranasally inoculated with SARS-CoV-2. Transient viral infection was observed in seven (78%) of nine inoculated fruit bats, with virus RNA detected in the respiratory tract. Furthermore, transmission in one of three bats was due to contact with SARS-CoV-2 inoculated bats, in which virus replication also occurred in the upper respiratory tract. Unlike the two studies mentioned above, in this most recent study, SARS-CoV-2 inoculated bats developed rhinitis, which is characterized by irritation and inflammation of the respiratory epithelium. The association between the presence of viral antigens and rhinitis revealed virus replication sites in the respiratory tract tissues. Nevertheless, a weak immune response was identified in all inoculated bats after the 8th day.

This study is of utmost significance as it reflects that bat-to-bat transmission is conceivable. Moreover, *R. aegyptiacus* can be considered a reservoir host and, therefore, could be helpful as an experimental model for the investigation of a potential reservoir host. However, it should be clarified that this species is assuredly not the original reservoir of SARS-CoV-2 as this bat species do not inhabit Hubei, a province of China that was the epicenter of the SARS-CoV-2 pandemic.

Last but not least, there are differences between human and bat immune systems; therefore, bats might not be the most suitable model organism for therapeutic medical trials [57].

NOVEL CORONAVIRUS-ASSOCIATED DISEASES AND THEIR POSSIBLE RELATIONSHIP WITH BAT CORONAVIRUSES

Over the past 20 years, several CoVs have been detected not only in wild animals but also in livestock and humans. Four high-risk pathogenic β-CoVs are noteworthy: The severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002; the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012; the swine acute diarrhea syndrome coronavirus (SADS-CoV) in 2017; and the most recent, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) in December 2019 [58].

SARS-CoV originated in China and spread to other countries. During its pandemic period (between 2002 and 2003), approximately 8000 individuals were infected with an overall mortality rate of 10% [59]. In 2013, a bat SARS-like coronavirus that uses the angiotensin-converting enzyme 2 (ACE2) receptor was isolated, providing conclusive evidence that bats were the most likely origin for SARS-CoV as the ACE2 receptor serves as an entry point for the coronavirus to infect human cells [60].

From its emergence in 2012 in the Middle East until March 2020, MERS-CoV has spread to 27 countries with 2521 laboratory-confirmed infection cases and 866 MERS-CoV-associated deaths, according to the World Health Organization (WHO) [61]. It has been recognized that Middle East dromedary camels had the role as a zoonotic transmission source for human

MERS-CoV [62]. Both SARS-CoV and MERS-CoV are believed to have a common lineage with bat coronaviruses, and both viruses have adapted to new hosts, such as palm civets [63] or dromedary camels [64], from which viral dissemination has occurred, resulting in a succession of human-human infections. Persistent interspecies recombination of the virus can trigger the development of a novel infectious coronavirus for transmission to humans.

The swine acute diarrhea syndrome coronavirus (SADS-CoV) was responsible for the third large-scale outbreak in 2017. Although the fatal disease exclusively affected pigs, it should not preclude the possibility of cross-species transmission to humans as *Rhinolophus* bats interact with both livestock and humans. In addition, SADS-CoVs have been frequently found in *Rhinolophus* bats, with the isolates showing a high genetic diversity with SARS-related CoVs [29].

Last but not least, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which started in Wuhan, China in December 2019, was declared a pandemic on March 11, 2020 by The World Health Organization [58]. Similar to SARS-CoV and MERS-CoV, SARS-CoV-2 is closely related to β-CoVs found in bats [65]. Moreover, bats can also harbor α-CoVs which are associated with pathogenic human 229E- and NL63-CoVs. It has been suggested that coronavirus NL63 is a recombinant formed between NL63-like viruses circulating in *Triaenops* bats and 229E-like viruses circulating in *Hipposideros* bats [20]. To sum up, the first 20 years of the twenty-first century have been characterized by the arrival of novel fatal human coronaviruses diseases which presumably have a bat origin. Furthermore, livestock and even domestic animals may have key roles as intermediate hosts allowing virus transmission from natural hosts to humans.

LEARNING TO PREDICT A NOVEL CORONAVIRUS OUTBREAK AND DISEASE SPREAD

Due to the presence of bat coronavirus-linked diseases that have had a severe impact on human society in the last 20 years, it can be assumed that a novel bat-borne coronavirus will arise and cause a future disease outbreak. Based on that supposition and prevalence of coronavirus-bearing bats, Southeast Asia is a probable region for the detection of novel CoVs. Regardless, the challenging questions are when and where a novel coronavirus will emerge; answers to those questions would help prevent such an outbreak. Some common factors should be taken into consideration when predicting a novel coronavirus outbreak.

First, bats harbor a great diversity of CoVs. It has been observed that bent-winged bats (*Miniopterus spp.*) can transport a notable variety of α-CoVs. For instance, the HKU8-CoV, which was first characterized circulating in *M. pusillus* in Hong Kong in 2005, was later isolated from *M. magnate, M. fuliginosus*, and *M. schreibersii*. This virus has spread in Hong Kong and disseminated to various provinces in China, such as Guangdong, Yunnan, Fujian, and Hubei, indicating the HKU8-CoV has a high genetic diversity [29,66]. This case reveals the necessity of understanding hotspot distribution and coronavirus transmission to avoid a future outbreak.

A second factor to be considered when predicting the next coronavirus outbreak is knowledge specific to a bat species and its distribution. Though it is recognized that several CoVs have not provoked viral outbreaks, they should still be monitored. China has acquired experience from the preceding SARS-CoV in 2002, becoming knowledgeable in methods

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to tackle sanitary health emergencies. This background allowed China to have an assertive response to the SARS-CoV-2 pandemic [67].

If prevention of a novel virus outbreak has not been successful despite considering the previous factors, lessons can be learned from the spread of SARS-CoV2 on methods to control or avoid a potential pandemic. Like the outbreak of SARS-CoV in China, Saudi Arabia struggled with the outbreak of MERS-CoV in 2012, and that virus remains endemic in that country to the present; thus, Saudi Arabia has gained exceptional experience in the virus control field [68]. Mathematical models and simulations have been used to predict the evolution of the 2019 novel coronavirus disease (COVID-19) epidemic at local levels in Saudi Arabia. These models have been beneficial as they provide valuable information about the intensity and severity of the disease spread. Mathematical modeling has also been helpful in the prediction of other recent epidemics such as Foot-and-Mouth Disease (FMD), SARS, Zika, and Ebola [69-71].

The Autoregressive Integrated Moving Average (ARIMA) model was successfully employed to estimate the daily confirmed cases of COVID-19 occurring between April 21 and May 21, 2020 in Saudi Arabia. The comparison was based on the confirmed daily case data provided by the Saudi Ministry of Health. Alzahrani et al. [72] predicted that by May 21, 2020, the daily case number would be 7668, with a daily cumulative case number of over 127,000 by the end of May 2020. Interestingly, the ARIMA model produced realistic estimates that were close to the actual situation. Spain and Italy, two countries severely affected by the COVID-19 pandemic also used the ARIMA model, with the predicted daily number of cases being acceptably precise compared to the actual case numbers [73]. Though the ARIMA model has been shown to be an excellent method for predicting outbreak evolution, the model has some disadvantages, such as not providing automatic updates and having a linear-based model structure while the disease relief problem is nonlinear; thus, diminishing the expected accuracy of the results. The inclusion of more available data for ARIMA model training can significantly contribute to the development of more precise predictions [72].

Finally, at the beginning of the COVID-19 outbreak, an innovative prediction method based on social media search indices (SMSI) was developed. The SMSI prediction method utilizes search words such as dry cough, fever, chest distress, coronavirus, and pneumonia to forecast the number of new suspected or confirmed cases. The new suspected and confirmed numbers of SARS-CoV2 infection cases were correlated strongly with a lagged series of SMSI. Though SMSI could become a potential predictor of the number of SARS-CoV2 infections, there are some limitations, such as the presence of various respiratory diseases with similar symptoms, that could undoubtedly bias or distort the SMSI model results [74].

CONCLUSIONS

In conclusion, the SARS-CoV2 pandemic has highlighted the need to strengthen our knowledge and comprehension of bat CoVs. It is evident that, among mammals, bats are a group that harbors the broadest range of CoVs; therefore, other CoVs that affect vertebrates, including human CoVs, are believed to have had their origin in bat CoVs. Unfortunately, we cannot keep the biological process of viral evolution from continuing; nevertheless, we certainly can reshape our current social and cultural habits to diminish the human impact of bat-origin CoVs. Moreover, if countermeasures are not adopted to tackle the deterioration of areas vital for wildlife, resulting from excessive agricultural exploitation and boundless

urbanization, then it should not be a surprise that we will be destined to face more regularly novel health crises that originat from wild animal–human interactions, particularly those between bats and humans.

It is undeniable that we need to deepen our understanding of how antiviral responses in bats have developed throughout evolution. Insights on this subject would allow us to develop novel strategies to identify drug targets not only in spill-over species such as bats but also in humans. Finally, statistical modeling has been demonstrated to be helpful in elucidating the characteristics of an outbreak and, therefore, in predicting more accurately its future tendency. Such mathematical models can provide a valuable perspective on an ongoing pandemic situation, thus, enabling authorities to make assertive decisions on tackling the pandemic while limiting its impact on society, the economy, and the healthcare systems.

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