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NARRATIVE REVIEW IN PUBLIC HEALTH

The relationship between bats and human coronavirus: An exploratory review

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Abstract

Introduction: Bats are known to harbour several coronaviruses including the progenitor of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which has caused COVID-19 pandemic. The emergence of SARS-CoV-2 has unwittingly fueled widespread apprehension and fear in the general public about bats. Aim of this paper was to review human coronaviruses in bats, the possible transmission dynamics of bat-borne viruses, and the impact of deforestation and climate change on bats.

Methods: A narrative review was conducted by using electronic databases- PubMed/Medline, Google scholar, Wiley Online Library, Semantic Scholar, and medXiriv- for searching all types of peer-reviewed and not peer-reviewed articles in English language, published from 2002 to 2020. All the findings and observations in this review were listed in references and main findings were summarized in a table.

Results: Certain species of bats are being progressively acknowledged as important natural reservoirs for several groups of viruses; some of which cause epidemics. Anthropogenic activities like encroachment of wildlife habitat, deforestation, developmental activities and close encounter with wild animals, cause disturbances in ecosystem functioning. This ecological imbalance threatens the bat populations and creates selection pressure leading to random mutations in the viruses. This may eventually cause viral spillover to humans and other animal hosts due to forced proximity, leading to outbreaks of novel diseases. Although bats are considered likely reservoirs of most of the human coronaviruses causing epidemics, yet they cannot be considered as a public health threat as the transmission dynamics is influenced by human behavior/ activities.

Conclusion: The complex eco-epidemiological situation calls for a judicious approach in assessing the role of bats in nature. Bats, on their own, may not pose public health threat, however there is a need to adopt comprehensive environmental health management policies based on the principles of conservation medicine to address this likely public health threat from bats.

KEY WORDS: Human Coronaviruses, Public health threat, Deforestation, Threatened Bat population, Ecological imbalance.

Riassunto

Introduzione: È noto che i pipistrelli ospitano diversi coronavirus incluso il progenitore del virus SARS-CoV-2, che ha causato la pandemia da COVID-19. La comparsa del SARS-CoV-2 ha inconsapevolmente alimentato una diffusa apprensione e paura nell'opinione pubblica dei pipistrelli. Questo lavoro ha l'obiettivo di fare una revisione sui coronavirus umani dei pipistrelli, le possibili dinamichedi trasmissione dei virus che hanno origine nei pipistrelli, e limpatto della deforestazione e dei cambiamenti climatici sui pipistrelli.
Metodi: Una revisione narrativa è stata condotta attraverso i database PubMed/Medline, Google scholar, medXiriv,Wiley Online Library, Semantic Scholar, per la ricerca di articoli di tutti i tipi, scritti in inglese, sia soggetti a revisione paritaria che non, pubblicati dal 2002 al 2020. Tutti i risultati e le osservazioni sono listati come da bibliografia e raccolte in una tabella dei risultati.
Risultati: Certe specie di pipistrelli sono stati progressivamente riconosciuti come un importante riserva naturale di divrsi gruppi di virus, alcuni dei quali causano epidemie. Le attività antropogeniche come l'invasione di habitat selvatici, la deforestazione, le attività di sviluppo e la stretta vicinanza con animali selvatici causano alterazioni nel funzionamento dell'ecosistema. Questo sbilanciamento ecologico minaccia le popolazioni di pipistrelli e crea una pressione selettiva che porta a mutazioni casuali nei virus. Questo può alla fine causare un effetto "spillover" nei virus con la trasmissione agli uomini e ad altri animali ospiti a causa della vicinanza forzata, che porta all'insorgenza di nuove malattie. Sebbene i pipistrelli siano considerati probabili serbatoi della maggior parte dei coronavirus umani che causano epidemie, tuttavia essi non possono essere considerati come una minaccia per la salute pubblica dal momento che le dinamiche relative alla trasmissione virale sono influenzate dalle attività e dai comportamenti umani.
Conclusione: La complessa situazione eco-epidemiologica invita ad un approccio giudizioso nella valutazione del ruolo dei pipistrelli in natura. I pipistrelli di per sé possono non essere una minaccia per la salute pubblica, tuttavia, c'è la necessità di adottare politiche di gestione sanitaria ed ambientali globali basate sui principi della medicina di conservazione per affrontare questa probabile minaccia per la salute pubblica che viene dai pipistrelli.

TAKE-HOME MESSAGE

Bats are essential ecosystem service providers and do not pose a public health threat, provided their populations are not threatened by the destruction of their natural habitats. Adoption of sustainable environmental health management policies based on the principles of conservation medicine will undoubtedly address the issue of spillover of zoonotic viruses and prevent novel diseases outbreaks like COVID-19 pandemic.

Competing interests - none declared.

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INTRODUCTION

Bats are a highly diversified yet distinctive group of mammals belonging to the order *Chiroptera* (meaning 'hand-wings' in Greek), which is the second largest order in class mammalia with respect to species number [1]. Thus far, bats constitute 20% of all mammalian species with more than 1,300 species across six continents [1]. Bats are an ecologically important group having various exceptional biological attributes that are not only vital for the global ecosystem but also for their role in seed dispersal and pollination [2]. Bats tend to maintain constant contact with humans by roosting in human-made constructions and feeding or resting on fruit trees or foraging on insects around light poles. Additionally, bats and humans both have many identical characteristics including physiological and immunological traits [3]. In the last couple of decades, certain species of bats are being progressively acknowledged as important natural reservoirs for several viruses [4]. It has been assumed that bats serve as reservoir hosts for the progenitor of SARS-CoV-2, supported by the genomic similarities between SARS-CoV-2 and bat SARS-CoV-like coronaviruses [5, 6]. Whole genome-wide nucleotide sequence analysis of SARS-CoV-2 revealed that it is 96% similar to a bat CoV (SARS r-Ra-Bat-CoV- RaTG13) [7, 8]. Viruses and viral subtypes of specific families, such as coronaviruses (CoVs), have been detected late with a considerable proportion being formerly unrecognized [3]. The recent emergence of many consequential zoonotic infections from bats, including Ebola, rabies, Nipah virus (NiV), Hendra virus and SARS-coronavirus, is in agreement with the general observation that bats undoubtedly are an important source of zoonoses, be they are existing, emerging or yet to be discovered [9]. Collectively, zoonotic viruses of more than 15 virus families have been recognized in atleast 12 bat families around the world [10–12]. Aim of this paper was to review human coronaviruses in bats, the possible transmission dynamics of bat-borne viruses, and the impact of deforestation and climate change on bats.

METHODS

A non-systematic or narrative review was conducted and research studies were drawn from a literature search which targeted peer-reviewed journal articles. The following databases were explored: PubMed, Google scholar, medXiriv, Wiley Online Library, and Semantic Scholar. Data searching period was comprised between 2002 to 2020. Both not peer-reviewed and peer-reviewed journal articles searched and used were in English language. These databases represent a varied range of disciplines allied to emergence of viral zoonosis, coronaviruses, bats, and public health. The search was initially conducted on PubMed using Medical Subject Headings (MeSH) terms such as, 'human coronaviruses', 'bats', 'public health threat', 'deforestation', 'climate change', 'conservation medicine', 'RNA viruses', by different combinations. After that, the relevant keywords searchable in the article titles and/or abstracts were added to expand the scope of search. The same approach to keyword searching was done for other databases as well. Additionally, a manual search of Google Scholar was conducted to review additional research articles. All the findings and observations in this review regarding the focused topic are based on published information as listed in the references and main findings are summarized in a Table.

RESULTS

Human coronaviruses in bats

After the Severe Acute Respiratory Syndrome (SARS) epidemic in 2003, more than 30 bat coronaviruses have been recognized till date and have become a focus of global research [13-26]. To date, there are seven human coronaviruses with the recent emergence of SARS-CoV-2 in the Hubei Province, China [27]. Coronaviruses may have a mild or lethal impact, HCoV-OC43, HCoV-HKU1, HCoV- 229E, and HCoV-NL63 are known to cause mild human diseases such as common cough and cold [28] whereas SARS-CoV, MERS-CoV, andSARS-CoV-2 are lethal coronaviruses [29–31]. It has been assumed by molecular clock analysis that the ancestors of HCoV-229E and HCoVNL63 might have had a bat origin. The most recent common ancestor of HCoV-229E has been found in leaf-nosed bat (*Hipposideros caffer ruber*) in Ghana, which presumptively diverged over two hundred years ago to a Bat-CoV [32]. HCoV-NL63 assumed to have crossed the species barrier since originating about over five hundred years ago in bats [33]. Hitherto the molecular analysis of genomes suggests HCoV-OC43 and HCoV-HKU1 may have not likely originated from bats [33]. Between the years 2002-2003 SARS-CoV was isolated from southern China and subsequently spread throughout the world [34]. The report of the first bat SARS-related CoV (SARS-CoV) in 2005 showed an immediate relatedness of the human SARS-CoV to the bat SARS like-CoV thus speculating a bat origin of the former (Table 1) [29]. Since 2012 another highly pathogenic β-CoV, namely Middle East respiratory syndrome coronavirus (MERS-CoV), has caused pandemics in humans [30]. Several β-CoVs closely related to the MERS-CoV have been found in dromedary camels and humans (Table 1) [13]. Although yet to be confirmed, multiple surveillance and phylogenetic studies undertaken so far support the speculation of suspected bat origin of MERS-CoV [35]. The current evidence available to date decisively indicates that SARS-CoV-2 belongs to the species of SARS-CoV [7]. It has further apprehended that SARS-CoV-2 has likely originated from bats considering 96% homology of SARS-CoV-2 with a bat coronavirus SARSr-Ra-Bat-CoV- RaTG13 (Table 1) [8].

Possible transmission dynamics of bat-borne viruses

Transmission of the virus from bats to humans can take place directly or through intermediate hosts [40]. For all the SARS outbreaks, bats were incriminated as a possible source of origin, with the viruses occasionally requiring an intermediate host before being transmitted to humans [41]. Urine, feces, and saliva excreted by bats (Figure 1), around trees where they feed or roost may contribute to the spillover dynamics of coronaviruses [42]. Bats cannot ingest large amounts of foods; therefore, they extract nutrients by chewing fruits and spitting the residues [2]. The animals sniffing on the ground for food can thus consume these partially digested foods which may infect them and potentiate them further as intermediate hosts [2]. The same has been seen for the animals that sniff in an attempt to avoid feces and urine, as they unwillingly acquire viruses from these excreta [42]. Other routes of transmission include consumption of bats by their natural predators depending on their locations. Weasels and raccoons have been identified as bat predators in some locations and interestingly SARS-CoV was also detected in raccoon dogs in a Chinese wet market [43,44]. Direct transmission from bat to human can occur through the ingestion of meat, as in some areas bats are a food source, or through bats bite as evident in case of rabies virus (Figure1) [26, 45].

Impact of deforestation and climate change on bats

At the present time, human activities such as logging, road construction, mining, and agricultural development constitute formidable reasons for deforestation [46]. Emergent viruses like SARS, Ebola, and other viruses of bats are associated with deforestation [47]. Deforestation of natural habitats consequently affects ecologic habitats of bats thereby, changing the reservoir abundances and altering the transmission dynamics [48]. Conversion of natural habitat largely into agricultural farmland forces the bat populations to congregate at patches provided with resources they need [40]. Unlike highly selective natural environments these patches in the vicinity of the human population are diverse and are acceptable by a wide range of bat species, usually not encountered together, hence, chances of inter-specific viral transmission escalate [49,50]. Likewise, viruses have found to circulate within different wild hosts and subsequently ‘jump’ the species barrier, ending up in humans, making them ultimate hosts. Cli-

Table 1. Human coronavirus and related coronaviruses in bats.

Authors and year	**Coronavirus**	**Bat species**	**Main findings of the study**
Li et al., 2005 [44]	SARS-CoV	*Rhinolophus sinicus* (Chinese horseshoe bat)	Antibody for SARS-CoV was prevalent in serum samples and cDNA from throat and fecal matter of Chinese horseshoe bat.
Li et al., 2005 [44]	SARS-CoV	*Rhinolophus pearsonii* (Pearson's horseshoe bat)	Prevalence of SARS-CoV antibody in throat and fecal matter of Pearson's horseshoe bat was detected by serum and cDNA analysis.
Li et al., 2005 [44]	SARS-CoV	*Rhinolophus macrotis* (Big-eared horseshoe bat)	SARS-CoV antibody was prevalent in serum samples and cDNA from throat and fecal matter of big-eared horseshoe bats.
Woo et al., 2006 [17]	Bat-SARS-CoV	*Rhinolophus sinicus* (Chinese horseshoe bat)	CoV related to SARS-CoV was isolated from anal swab of Chinese horseshoe bat.
Memish et al., 2013 [36]	MERS-CoV	*Taphozous perforates* (Egyptian tomb bat)	CoV identified in rectal swab samples or fecal pellets and from roost feces of Egyptian tomb bat has 100% nucleotide sequence identity with human MERS-CoV.
Annan et al., 2013 [37]	MERS-CoV related CoV	*Nycteris Gambiensis* (Slit faced bat)	CoV with close relation to MERS-CoV was detected in fecal samples of Slit faced bat, mostly in juvenile and lactating female bats.
Annan et al., 2013 [37]	MERS-CoV related CoV	*Pipistrellus pipistrellus* (Common pipistrelle)	High concentration of CoV with close relation to MERS-CoV was detected in feces of Common pipistrelle bat.
Annan et al., 2013 [37]	MERS-CoV related CoV	*Pipistrellus pygmaeus* (Sporano pipistrelle)	CoV with close relation to MERS-CoV was detected from the fecal samples of Sporano pipistrelle bat.
Yang et al., 2014 [22]	MERS-CoV related CoV	*Vespertilio superans* (Asian particoloured bat)	60%–97% amino acid similarity of CoV was identified in anal swab samples of Asian particoloured bat to MERS-CoV.
De Benedictis et al., 2014 [38]	MERS-CoV related CoV	*Eptesicus serotinus* (Serotine bat)	Italian lineage C beta-CoV identified in anal swabs of Serotine bat had 96.9 % amino acid identity to MERS-CoV.
Anthony et al., 2013 [39]	MERS-CoV related CoV	*Nyctinomops lacticaudatus* (Broad-eared bat)	The CoV identified in rectal swabs and oral swabs of Broad-eared bat had 96.5% amino acid identity to the MERS-CoV.
Huynh et al., 2012 [33]	HCoV-NL63 related CoV	*Perimyotis subflavus* (Tricolored bat)	Detection of nucleic acid sequences that potentially indicate the presence of CoV in fecal samples of tricolored bats that was presumed to share recent common ancestry with HCoV-NL63.
Pfefferle et al., 2009 [32]	HCoV-229E related CoV	*Hipposideros caffer ruber* (Leaf-nosed bat)	Molecular clock analysis revealed that CoV detected infecal pellets or swabs of leaf- nosed bats share the most recent common ancestry with HCoV-229.
Lau et al., 2020 [8]	SARS-CoV-2 related CoV (SARSr-Ra-Bat-CoV-RaTG13)	*Rhinolophus affinis* (Intermediate horseshoe bat)	CoV detected in Intermediate horseshoe bat had 96.1% genome identity with SARS-CoV-2.
Lau et al., 2020 [8]	SARS-CoV-2 related CoV (SARSr-Rp-BatCoV-ZXC21/ZC45)	*Rhinolophus pusillus* (Least horseshoe bat)	The CoV identified by pan-coronavirus reverse transcription (RT)-PCR assay, in the Least horseshoe bat had 87.6%–87.8% genome sequence identities with SARS-CoV-2.

mate change has been implicated as a potential factor initiating such jumps [51]. It has been documented that climate change not only impacts host immunocompetence, which in turn affects pathogen load, but also affects densities or species composition of host and vector communities along with the contact rates between zoonotic hosts and humans [51]. The survivability of certain viruses may get supported by a cold and dry environment and, subsequently, they may find some ways to cross the species barrier, which is known as 'viral chatter' [52]. Studies on SARS revealed an association of the virus with temperature; viral growth was found enhanced with a temperature of 16°C to 28°C [41]. The influence of rising or declining environmental temperature on the immune system of human hosts

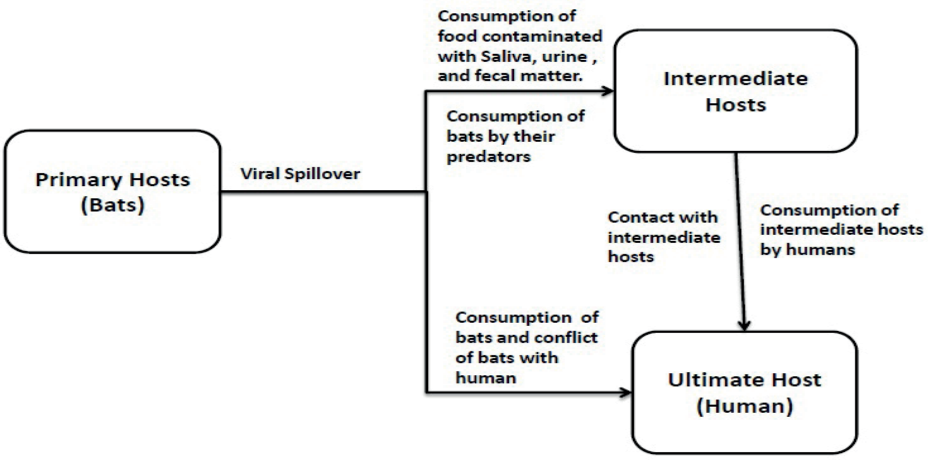

Figure 1. Possible transmission routes of bat-borne viruses.

is evident by the increased number of SARS cases especially in colder climates [53].

DISCUSSION

About 80% of emergent human viruses appear to be of zoonotic origin [54]. Virtually all animals harbor viruses of different kinds but all of them have not been found to contribute viral spillover events. Bats are unique to some extent as they are likely to be infected with more zoonotic viruses per host species than others [10]. Many serious zoonotic infections have originated from bats, including SARS-coronavirus [9]. Among seven human coronaviruses, five are postulated to have bat origins which include SARS-CoV, MERS-CoV, and SARS-CoV-2, causing SARS, MERS epidemics and COVID-19 pandemic, respectively [4, 8, 32, 33, 36]. Prior to the SARS outbreak in 2003, coronaviruses were only known to be the cause of the common cold. It has been speculated that SARS-CoV emerged from bats and subsequently passed to humans via intermediate hosts [41]. However, whether SARS-CoV-2 has been transmitted directly from bats or by an intermediate host requires further confirmation [55]. The similarities between the presumed ancestries of bat harbored zoonotic viruses indicate a long co-evolutionary history of bat and virus. It has been perceived that bat-associated viruses evolved with and within bats by using the conserved replication cellular receptors and biochemical pathways of mammals, thereby spreading out to other mammals with enhanced capacity of transmission [4]. For the transmission of the virus from bat to human, a hierarchy of favorable conditions is required which includes distribution of reservoir hosts, virulence, and maintenance of viruses within these hosts, exposure, and susceptibility of recipient hosts. However, spillover also requires viral shedding from bats and the sustainability of the virus in the environment [42]. Suppression of host defense system in bats, for various reasons including environmental stress, can lead to increased viral load in specific organs and subsequently lead to viral shedding through urine, saliva, and fecal matters [56]. According to a school of scientists, animals may get viruses by consuming fruits that had been partially eaten by bats thus passing the virus to humans, which has been witnessed in the case of pigs [57]. However, this hypothesis was tentatively rejected by another school of thought based on the fact that pellets discarded by bats comprise indigestible fibers and seeds with low nutritional value, therefore; other animals may not consider these as food [58]. More than 200 viruses have been associated with bats, and almost all are RNA viruses [2, 3, 59]. Sequence analyses of viral RNA suggest some viruses like coronaviruses may get genes by frequently recombining with other closely related viruses [60]. Moreover, a possibility appears whereby bats or human hosts can act as 'Mixing pot' of evolutionarily significant recombination events [61]. There are many insectivorous bats consuming lepidopteron insects including moths as diet [62]. Several plant viruses have been found to circulate and propagate within these lepidopterans [63]. Plant viruses have also been detected in the fecal matter of bats [64]. Nonetheless, it is important to determine whether the presence of plant viruses in bats contributes to human disease transmission and if it does, then, to what extent.

Existing literature cites that from a total of 175 genera of bats [65,66], only 37 genera are known to harbor viruses [3]. Bats are, however, essential participants in maintaining the global ecosystem, and humans are also benefited from their presence in several ways. Their involvement in the dispersal of seeds and pollination contributes to the restoration of forests and pollination of wild plants along with agricultural plants. Furthermore, bats are the important predators of night insects, including pests. Even nitrogen-rich bat-guano of bats is used as biological fertilizer [2]. In tropical countries, biodiversity has been threatened by the conversion of natural habitats to agricultural and pastoral land [67]. Needless to emphasize that cropland extension has largely come at the cost of undamaged old-growth forests [68]. It is noteworthy that alteration in natural ecosystems can likely result in the emergence of zoonotic diseases from bats [69]. The demolition of natural feeding and roosting habitats due to urbanization and agricultural land expansion has obligated bats into urban and farming areas, intensifying the chances of encounter and conflict between bats, humans, and domestic animals [70]. It is a well-documented fact that, in the case of Nipah virus (NiV), deforestation triggered the encroachment of bats into agricultural areas, leading to the transmission of the virus from bats to domestic pigs and then to humans [71]. It is likely that such transmission may be occurring in the case of human coronaviruses as well, but this needs validation through further studies. Bats are known to be highly sensitive to landscape modifications and require large forested areas for foraging [42] therefore, any changes in natural habitats coupled with host abundances, due to climate change, can constitute an important determining factor in disease dynamics [51]. Multiple host species can have different habitat requirements and are capable of being infected by the same pathogen, thus contributing to the geographical overlap of viruses, resulting in intensified interaction with susceptible hosts [72]. Likewise different species of bats harboring different viruses can get together as consequences of habitat loss leading to an increase in reservoir abundance [49,50]. The frequent recombination of RNA viruses inside the hosts may result in mutant variants that are detectable in the case of coronaviruses [60]. These variants may subsequently be selected by natural selection for their great ability of adaptation in changing environmental conditions [2, 3, 59] resulting in the emergence of new zoonoses. The interrelationship between deforestation resultant in biodiversity loss and emerging zoonotic diseases is complex; these factors greatly influence the emergence of novel pathogens and disease dynamics in multiple ways. 'Conservation medicine' [73] focuses on sustainable environmental health as a whole, encompassing humans and the flora and fauna through developing health management policies and practices. This inclusive approach of conservation medicine could be a useful and effective mechanism for preventing the spillover of novel zoonotic viruses, thereby reducing the chances of diseases caused by them. This assumption needs further validation by programmed studies directed in this direction.

CONCLUSION

Bats, since time immemorial, have been known as natural reservoir hosts of a variety of viruses including some viruses of epidemic potential. It is evident that these viruses co-existed and co-evolved with bats by means of natural selection, making bats the primary reservoirs. Severe epidemics over the last couple of decades like SARS, MERS, and COVID-19 has led to very plausible speculation of their likely origin from the ancestral group of coronaviruses found in bats. During the COVID-19 pandemic, a general perception has arisen in the society that bats are public health threats because of their capability to harbor and disseminate viral pathogens. Although we cannot deny nor ignore the possible threats from the emerging viruses harbored by bats, however, at the same time it is also important to remember that the anthropogenic activities like encroachment of wildlife habitat, man-animal encounter, consumption of wild animal, rampant deforestation for urbanization and other developmental projects coupled with climate change has threatened and jeopardized the bat population as well. This ecological imbalance has likely created selection pressure followed by random mutation in the viruses harbored by bats, which has ultimately led to viral spillover to humans and other animal hosts. Based on analysis of the lineage-specific selection pressure, SARS Coronaviruses in bats and humans were seen to be under significant positive selection, thereby demonstrating an instance of recent interspecies transmission. Moreover, a large proportion of bat species do not harbour such pathogenic viruses. Bats are in fact essential ecosystem service providers contributing to crop production and insect pest control. It is needless to emphasize that bats are not a public health security threat, provided their populations are not threatened. It is important to remind ourselves that in this complex eco-epidemiological situation we have to be judicious while assessing the role of bats in nature. It is imperative to formulate comprehensive scientific policies based on the principles of conservation medicine to holistically address the issues of public health security threat to humans as well as to the threatened bat populations. In order to maintain the ecological homeostasis of the wild environment, where the bats roost, it is important to consider conservation of biodiversity of the concerned area. Appropriate implementation of such policies and programs would be helpful in reducing the threat to both humans and bats, thereby establishing an environment for harmonious living with the wildlife.

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