Chapter 8

Bats, Bat-Borne Viruses, and Environmental Changes

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Additional information is available at the end of the chapter

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Abstract

During the past decade, bats were shown to a major source for new viruses. Among them are well known coronaviruses such as SRAS or MERS but also Ebola. At the same time, no direct infection from bat to human has been demonstrated. The dynamic of transmission of bat-borne viruses is therefore a complex process involving both sylvatic and urban cycles, and intermediate hosts not always identified. The threat potentially exists, and drivers must be sought for man-made environmental changes. Anthropized environments are mosaic landscapes attracting at the same place different bat species usually not found together. Anthropized landscape is also characterized by a higher density of bat-borne viruses. The threat of new bat-borne virus outbreaks has greatly increased in the recent years along with media anthropization and the extremely rapid deforestation process. Deforestation could be a major contributing factor to new viral emergences due to more frequent contacts of livestock and humans with bats possibly containing infectious viruses.

Keywords: bats, bat-borne viruses, environment, landscape change, anthropization, emergence

1. Introduction

Emerging infectious diseases (EIDs) remain a major threat to public health. Most EIDs described in humans have been shown to be of zoonotic origin. During the past decades, growing evidence that viruses causing EIDs in humans share identity or strong sequence homologies with viruses circulating in bats were reported; this result pushed the epidemiologist to focus their attention on these wild mammals in order to determine whether bats play a particular role as virus diversity reservoirs worldwide and to understand the state of the threat in a context of ecosystem change.

Taxonomically, bats are grouped in the order *Chiroptera* (Gr. *cheir*, hand; *pteron*, wing) and they are the only mammals with adaptation for powered flight on long distance. Although bats are outnumbered by rodents in species richness, they represent the second species richness in the mammal world with 1230 species—more than 20% of all mammals on earth—inhabiting a multitude of ecological niches [1]. Bats are currently known as important reservoirs of zoonotic viruses worldwide [2] and factors underlying high viral diversity remain the subject of speculation. Bats have sometimes been considered as enigmatic mammals having a particularly effective immune system or antiviral activity [2, 3]. Obviously, bats are not very different from other mammals, and several bat viruses can cause disease and death of bats; in example, a study performed on 486 deceased bats of 19 European Vespertilionidae species showed that two thirds of mortality were due to trauma or disease and that at least 12% of these mammals had succumbed to infectious diseases (19 died from bacterial infections; 5 died from viral infections caused by bat adenovirus AdV-2 or bat lyssavirus EBLV-1; 2 died from parasitic infections) [4]. Yet, numerous viruses apparently remain non-pathogenic in bats, likely due to a long process of co-evolution; although most of these viruses apparently do not affect bats health, some of them have been shown to severely affect wild and domestic mammals, as well as humans.

2. History

The fact that bats play a role as reservoir of human viruses was recognized during the first half of the twentieth century, when rabies was found in South and Central America [5]. The hypothesis that bat may act as a reservoir of viruses causing EIDs in humans was next acknowledge several decades later, during the second half of the twentieth century. Most genotypes of rabies or rabies-related virus within the *Lyssavirus* genus of the Rhabdoviridae family have been documented in bats [6]. In the recent years, bats have gained notoriety after being implicated in numerous EIDs. Bat-borne viruses that can affect humans and have caused EIDs in humans fall into different families: paramyxoviruses including Hendra viruses [7] and Nipah viruses [8]; Ebola hemorrhagic fever filoviruses [9]; Marburg hemorrhagic fever filoviruses [10] and sudden acute respiratory syndrome-like coronaviruses (SARS-CoV) [11]. Their list is probably far from complete. Interestingly, the powerful retroviral hosting ability of bats had likely contributed to shape mammalian retroviruses [12]. Furthermore, sialic acid receptors for avian and human influenza virus are found in the North American little brown bats, which could potentially facilitate the emergence of novel zoonotic strains [13].

In this context, it becomes urgent to resolve, as soon as possible, three essential questions, namely: Will bats help to serve as a source of pathogenic viruses for animals and humans with regard to pathogens that have already caused EIDs in humans? Are bats reservoirs for viruses that have not yet infected humans but could be at the origin of EIDs in the future? Could bats be considered as "living test tubes" in which new viruses could be developed through genomic exchanges and genetic drift? To answer these questions, it is essential to monitor bat

populations and to analyze the diversity of viruses circulating in these populations. Although informative, the study of circulating viruses in a few specimens and a particular ecosystem cannot account for the global dynamics of viral populations present in the different families of bats on the planet. The isolation and sequencing of viruses was an important step, but not enough performing to capture the extent of the phenomenon. Polymerase chain reaction (PCR), when primers were available, have also contributed to a better characterization of bat-borne viruses being related to viruses that have already produced EIDs in humans. More recently, high-throughput sequencing and metagenomic approaches have led to a quantum leap in surveillance and the quest for knowledge [14–17]. However, a global vision remains indispensable and the initiatives, which make it possible to compile the data of the various laboratories and to catalog them as comprehensively as possible, are welcome [18] (http://www.mgc.ac.cn/cgi-bin/DBatVir/main.cgi), in addition to other virus database such as the Virus-Host DB (http://www.genome.jp/virushostdb/; this database currently select 134/10028 items under "bat" query), the NCBI viral genome resources (https://www.ncbi.nlm.nih.gov/genome/viruses/; this database currently select 84 items under "bat" query) or Virus Pathogen resource, VIPR (https://www.viprbrc.org/brc/home.spg?decorator=vipr). It is worth noting that although bats are found on all continents except Antarctica [19], the accumulation of results is very variable from one continent to another. As shown in **Figure 1**, Asia is largely in the lead for data accumulation ahead of North America and Africa and next Europe and South America (**Figure 1A**). The preponderance of Chinese results for Asia's contribution is even more impressive (**Figure 1B**). Almost 60% (58.9%) of Asian articles originate from China, followed by Vietnam at 16.8%. All other contributing countries are below 7%, i.e. 6.5% for both Thailand and Cambodia. It is quite interesting to highlight the correlation between the number of publications and the geographical origin of scientific teams who publish them, because Asia/Southeast Asia is considered as one of the hotspot on the planet for the emergence of new viruses.

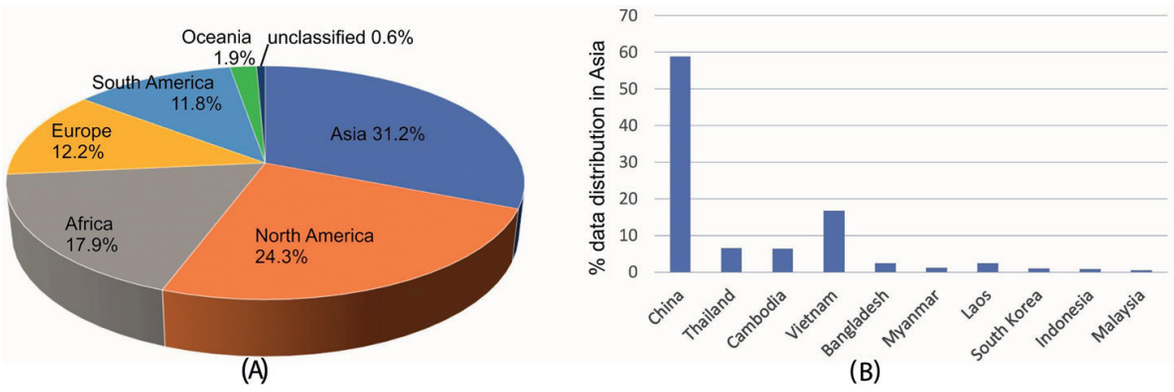

Figure 1. Data distribution. (A) Overall data distribution of bat-associated viruses by geographic region (Asia: 2274 publications; North America: 1772 publications; Africa: 1307 publications; Europe 891 publications; South America: 858 publications; Oceania: 142 publications; and unclassified: 47 publications). Adapted from the database of bat-associated viruses (http://www.mgc.ac.cn/cgi-bin/DBatVir/main.cgi). (B) Data distribution in Asia. China comes first with 1723 publications (58.9%), followed by Vietnam with 491 articles (16.8%), Thailand with 190 articles (6.5%) and Cambodia with 189 articles (6.5%) (http://www.mgc.ac.cn/cgi-bin/DBatVir/main.cgi, updated February 18, 2018).

3. Etiology and associated diseases

Globally, a small proportion of the approximately 55,000 annual human deaths caused by rabies virus are the result of infection by variants or virus associated with bats [19]. Human rabies caused by bat *lyssavirus* (genotype 1: rabies virus; genotype 2: Lagos bat virus; genotype 4: Duvenhage virus; genotype 5: European bat lyssavirus type 1, EBLV-1; genotype 6: European bat lyssavirus type 2, EBLV-2; genotype 7: Australian bat lyssavirus) was regularly reported in South and North America, Africa, Europe and Australia [20–22].

In 1994, an outbreak of an acute respiratory illness occurred in a human and 14 horses in Hendra, a suburb of Brisbane, Australia. These EIDs finally affected 2 humans and 22 horses [23]. Four additional outbreaks were observed during years 1994, 1999, and 2004, infecting two humans and five horses and killing all but one human. A virus of the *Paramyxoviridae* family, genus *Henipavirus*, carried by *Pteropus* bats, and named Hendra virus was shown to be the etiologic agent of this disease. Nipah virus (NiV), another member of the *Paramyxoviridae* family found in *Pteropus* bats, associated with encephalitis in humans, was discovered in an outbreak in Malaysia in 1998 that affected 283 persons and caused 109 deaths (case fatality rate 39%) [24]. Direct contact with infected pigs was identified as the predominant mode of human infection. Subsequently, outbreaks of NiV have been observed almost every year in Bangladesh [25] and occasionally in India [26]. Bangladesh outbreaks were shown to be linked to consumption of fresh data palm sap contaminated by NiV-containing *Pteropus* bats' secretions and excretions [27]. In 1997, another member of the bat-borne *Paramyxoviridae* family, described as Menangle virus, was isolated from stillborn piglets in Australia; two of 250 humans living in contact with the infected animal showed febrile illness with measles-like rash and had high titer of anti-Menangle virus antibodies [28]. These people never get in contact with flying foxes, suggesting that this bat-borne virus was transmitted to the humans after infection of pigs/piglets [29]. Before 2002, although coronaviruses (CoV) were known to be agents of respiratory infections in humans (e.g.; common winter cold), they lent little attention. Human CoV (HCoV) strongly gained in notoriety after being identified as responsible for the severe acute respiratory syndrome (SRAS) outbreak in humans [30]. SRAS emerged in 2002 in China and spread across 29 other countries, causing more than 8000 infected patients and almost 800 deaths worldwide (case fatality rate about 10%). Serological analysis of healthy human samples collected in Hong Kong in 2001 revealed a prevalence of 1.8%, suggesting that the circulation of SARS-related viruses had occurred prior to the 2003 epidemic. Indeed, SARS-like CoV circulating in Chinese horseshoe bats had spread and adapted to wild Himalayan palm-civet often sold as food in Chinese markets [31]. After mutation, this CoV adapted to humans and became able to spread from person-to-person. During SARS outbreaks in Toronto and Taiwan, certain persons were very efficient at transmitting SARS-CoV and were named "Superspreaders" [32]. A few years later, the emergent Middle East Bats Respiratory Syndrome (MERS)-CoV was reported in Saudi Arabia in 2012) [33]. Once again, the human MERS-CoV likely originated from a bat-CoV-related virus and was likely transmitted through camel-human contacts [34]. The MESR epidemics displayed

a limited spread to other countries in the Middle East (except in individuals traveling back from Middle East). So far, 2081 people were infected with MERS-CoV among which 722 died from the disease (case fatality rate 34.7%). It is worth noting that during the 2012–2014 outbreak of MERS-CoV, "superefficient" person-to-person transmission apparently did not occur. However, the MERS-CoV outbreak that affected the Republic of Korea in 2015 was caused by a single person (68 years old "index patient") who developed fever 2 weeks after returning from 2 weeks travel in the Middle East. Once back to Seoul, this person visited the Samsung Medical Centre on 17 May and was isolated the day after on suspicion of MESR before being finally diagnosed with MERS on 20 May. A total of 186 people were infected out of which 36 died; some 44.1% of the cases were patients exposed in hospitals, 32.8% were caregivers, and 13.4% were healthcare personnel. Interestingly, a total of 83.2% of the transmission events were epidemiologically linked to five "superspreaders," all of whom had pneumonia characterized at the first medical consultation. In August 2015, 1413 laboratory-confirmed cases of MERS have been reported worldwide of which 502 died [35]. The cause for superspreading events is still unclear and could be consequence of virus mutation, high viremia linked to higher level of virus shedding, environmental factors such as co-infection, or host-altered immune status. A recent study of a virus closely related to Middle East respiratory syndrome coronavirus (MERS-CoV) found in a *Pipistrellus* bat supports the bat-borne origin of MERS-Cov [36].

Ebola hemorrhagic fever is also caused by a zoonotic virus discovered during an epidemic outbreak that affected people in villages of Democratic Republic of Congo (DRC; more than 300 infected people) and Sudan (almost 300 people infected), in 1976 [37]. Ebola virus is responsible for a severe and frequently fatal illness characterized by a nonspecific viral syndrome followed by a fulminant septic shock, multi-organ failure, and coagulopathy resulting in severe bleeding complications). Though silent during a few years, Ebola virus continued to circulate in these regions and re-emerged in Sudan in 1979 (34 infected people) and Gabon and DRC in 1994–1995 (more than 350 infected people). Between 1996 and 2014, several outbreaks were reported in different African countries, each episode affecting from a few people to thousands for the 2014 epidemic, case fatality 52% [38].

Although the recent emergence of viruses known to be carried by bats have not led to very large epidemic outbreaks (a few hundred to a few thousand infected people), the fact that some of these viruses can adapt to spread from person-to-person, and the high mortality associated with these infections (case fatality frequently above 30% of infected persons) has contributed to consider them a major public health risk by international medical authorities. This partly explains why after a period of relative disorganization in the face of the threat (e.g. SARS, MERS and Ebola outbreaks), each emergence was subject of a rapid response by the health authorities. In some cases, treatment of the disease is largely limited to supportive therapy and requires appropriate control measures. This proved true for the 2014′ Ebola outbreak in West Africa, which was the largest in history. Ebola hemorrhagic fever was diagnosed in Guinea in December 2013 and outbreaks next appeared in Liberia, Nigeria, Senegal, and Mali. By 18 September 2014, WHO reported of 5335 cases with 2622 deaths (case fatality around 50%). Early 2015, additional cases were reported in Mali and

Sierra Leone. On April 2015, the Ebolavirus outbreaks had already resulted in more than 10,880 deaths among 26,277 cases [38]. On March 2016, WHO reported a total 11,323 deaths among 28,646 cases, indicating a decrease in the spreading of the virus in human. There is no direct evidence that bat is the reservoir for ebolavirus-inducing disease in humans. Yet, Ebola-related virus were found in tissues of several bats (the hammer-headed fruit bat: *Hypsignathus monstrosus*; the Franquet's epauletted bat: *Epomops franqueti*; and the little collared fruit bat: *Myonycteris torquata*) [9], and experimental infections of the Angola free-tail bat (*Mops condylurus*), little free-tail bat (*Chaerephon pumilus*), and Wahlberg's epauletted fruit bat (*Epomophorus wahlbergi*) with a Zaire strain of Ebola virus led to viral replication in these bats [39]. Widespread infection of cave-dwelling bats by Crimean Congo hemorrhagic fever virus (CCHFV) has also been reported, suggesting a role of bats in the life cycle and geographic dispersal of this virus [40].

It is generally admitted that bats are a source of high viral diversity that may directly or indirectly (following genomic recombination, gene mutations, gene duplication loss/gain) cause a new outbreak. Since the past 20 years, a massive international effort was devoted to the identification of viruses in different families of bats. As shown in **Figure 2**, the total number of bat-associated sequences in GenBank has grown exponentially in the last 20 years. A review of articles referring to bat-borne viruses (**Figure 3**) indicates that rabbies (55,000 persons infected each year, case fatality nearly 100%) is the most prominent topic with 2792 articles (33%). Surprisingly, as shown in **Figure 3A**, the virus family that rank second is *Coronaviridae* with 2622 articles (31%), while the total number of cases accumulated the different episodes remains relatively low (cumulative cases about 8000 individuals; mean case fatality around 10%). Moreover, the number of scientific report about virus family indicates that Coronavirus rank first in terms of publications when MeSH terms concern viruses and

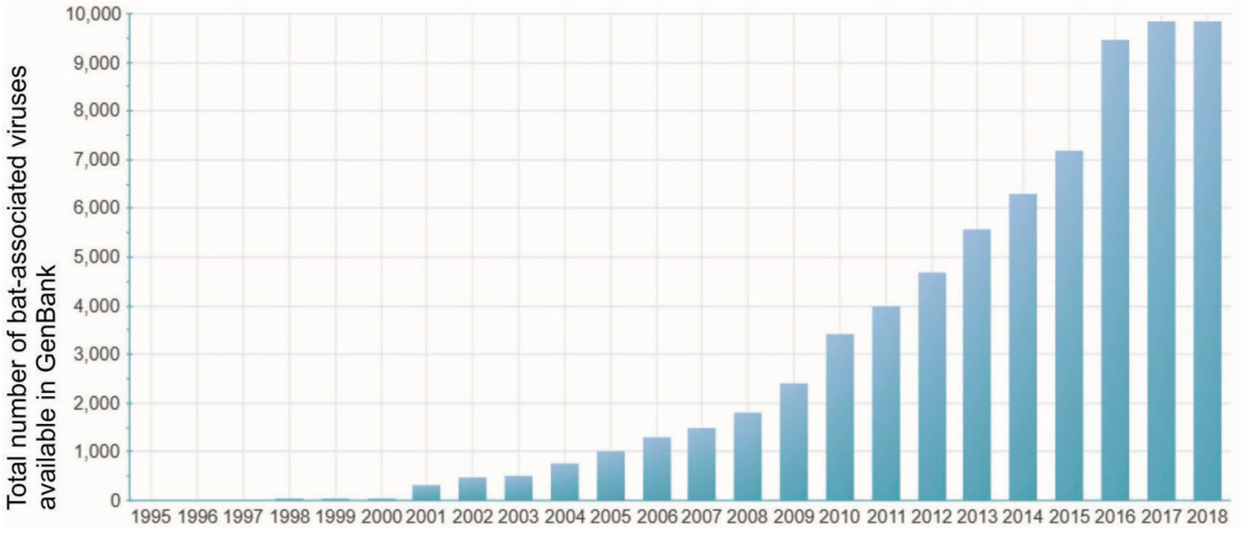

Figure 2. Data increase of bat-associated viruses during the past 20 years. This figure illustrates the total number of sequences of bat-associated viruses available in GenBank according to the database of bat-associated viruses (http://www.mgc.ac.cn/cgi-bin/DBatVir/main.cgi). During the same period (1997–2017), the total number of publications about bat-associated viruses in PubMed increased from 2 to 367 publications/year.

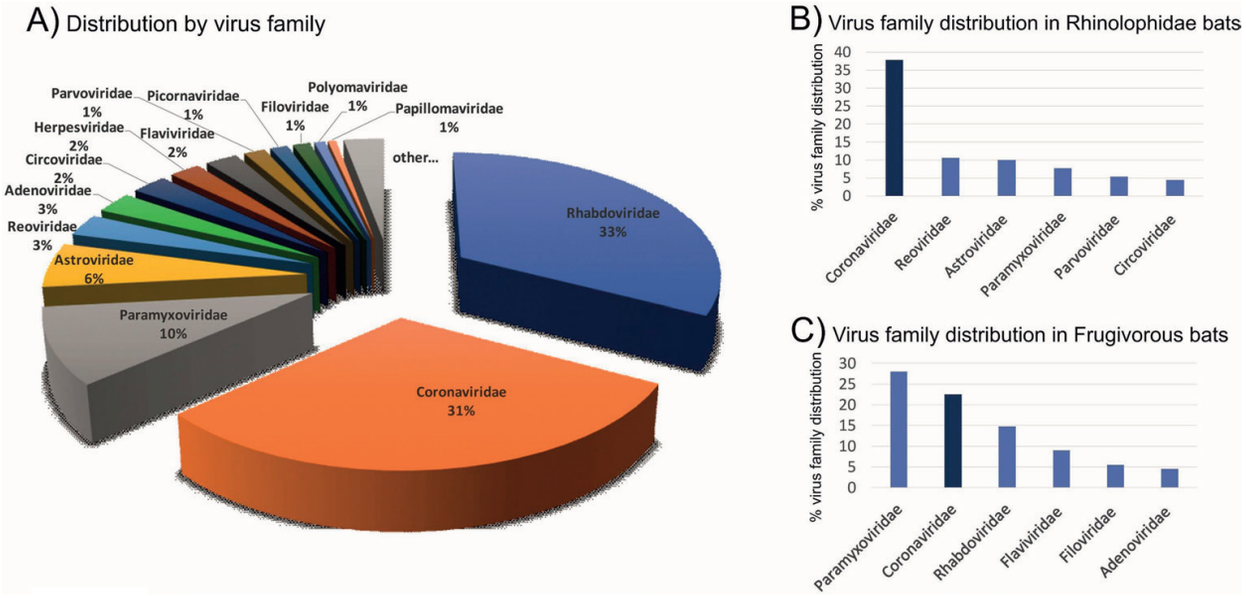

Figure 3. Distribution by virus family. (A) Overall data distribution by virus family. Adapted from the database of bat-associated viruses (http://www.mgc.ac.cn/cgi-bin/DBatVir/main.cgi, updated February, 18, 2018). Rhabdoviridae come first with 2792 articles (32.7%), followed by Coronaviridae with 2622 articles (30.7%), Paramyxoviridae with 839 articles (9.8%), Astroviridae with 494 articles (5.8%), Reoviridae with 244 articles (2.9%), Adenoviridae with 232 articles (2.7%), Circoviridae with 218 articles (2.6%), and Herpesviridae with 189 articles (2.2%). Others represent different virus families such as Flaviviridae (2.3%), Parvoviridae (1.5%), Picornaviridae (1.3%), Filoviridae (1.2%), Polyomaviridae (0.8%), Papillomaviridae (0.6%), and other virus families ranking 2.9%. (B) Ranking of virus family distribution (top 1–6) in Rhinolophidae. (C) Ranking of virus family distribution (top 1–6) in Frugivorous bats.

Rhinolophidae bats (**Figure 3B**) and second when MeSH terms concern viruses and frugivorous bats (**Figure 3C**). It suggests that the number of articles published concerning bat-borne virus does not correlate with the number of infected persons and the case fatality, but rather reflect the perception of a risk felt by the public authorities, health authorities, and funding agencies according to societal demand and presentation of the threat by the media. Even if the accumulation of knowledge through research works is probably influenced by these problems of perception of the risks, the example of coronavirus remains very interesting to tackle emergence phenomena. The increasing risk of pathogen transmission between bats, animals and humans in South East Asia is a consequence of the growing human population and of anthropization of environment (deforestation, agriculture) which have largely altered landscapes [41].

4. Coevolution between bats and viruses

The biological interaction of viruses and their hosts is usually antagonistic, with a delicate balance of actions and counteractions between host immune system and virus escape mechanisms. Parasite-induced reduction in host fitness enhances selection for host resistance

mechanisms. On the other hand, novel host defenses increase selection on the parasite. A tight genetic interaction between hosts and pathogens can lead to ongoing host-parasite coevolution, defined as the reciprocal evolution of interacting hosts and parasites [42]. The antagonistic coevolutionary arms race of parasite infectivity and host resistance leads to adaptations and counteradaptations in the coevolution and also has a central role in the evolution of host-parasite relationships in the microbial world [43]. A key consequence of coevolution is the impact on genetic diversity of host and parasite populations. The host-parasite coevolution is widely assumed to have a major influence on biological evolution by imposing a high selective pressure on both host and virus. Selected traits, genes involved, and the underlying selection dynamics represent central topics of interest for understanding host-parasite coevolution [44].

The evolution of bats is a very successful singular history among mammals that have produced an enormous diversity of species with high mobility and great longevity adapted to a great spectrum of environments [42]. Bats host more zoonotic viruses and more total viruses per species than rodents, despite the fact that there is a lot more known species of rodents [45]. Furthermore, bats harbor a significantly higher proportion of zoonotic viruses than all other mammalian orders [46]. The antagonistic coevolutionary arms race of parasite infectivity and host resistance leads to adaptations and counteradaptations in the coevolution and also has a central role in the evolution of host-parasite relationships in the microbial world [47]. The origin of bats is estimated at about 64 million years ago or following the Cretaceous-Tertiary boundary [48]. The millions of years of bat evolution might have given rise to the coevolution processes between host and pathogen. The antagonistic coevolution between infectivity of viruses and resistance of bats is still poorly known. The ability of bats to harbor extremely lethal viruses for humans without apparent morbidity and mortality has long been discussed. The lack of abnormal ethology observed in virus-infected bats may be due at the selection of resistance mechanisms.

The evolution of flight in bats has been accompanied by genetic changes to their immune systems to accommodate high metabolic rates. The increased metabolism and higher body temperatures of bats during flight might have enhanced their immune system, increasing resistance and thus increase the diversity of viruses they host [2, 49]. This increase of metabolic rate in bats is estimated to be 15- to 16-fold, when it is only sevenfold for running rodents and twofold for birds [2]. Marburg, Angola, Ebola, and Makona-WPGC07 viruses were shown to efficiently replicate at flight temperature of bats, i.e. 37 and 41°C, indicating that flight-related temporal elevation in temperature does not affect filovirus replication [50]. Furthermore, many bat species display a daily torpor with decrease of body temperature which might be a virus-resistance strategy, interfering with optimal virus replication [2]. Bats also display a unique interferon system (IFNs) that may explain the ability of bats to coexist with viruses [51]. Mammals have a large IFN locus comprising a family of IFN-α genes expressed following infection. Conversely, bats display a contracted IFN locus with only three functional IFN-α, but constitutively and permanently expressed [51]. This constitutive expression could turn to be a highly effective system for controlling viral replication and explain the resistance of bats to viruses. Differences have also been observed in the immune

response between bat species against the same virus. Important differences in percentage of seroconversion against European bat lyssavirus type 1 (EBLV-1) were observed between two species from two distinct families: *Rhinolophus ferrumequinum* (*Rhinolophidae*) and *Myotis myotis* (*Vespertilionidae*). The percentage of seropositive *Rhinolophus ferrumequinum* was much lower than that of *Myotis myotis* [45], suggesting differential rates of seroconversion. Turmelle et al. [52] reported that significant differences in seroconversion rates were found among bats depending on whether they had previously been infected, suggesting that long-term repeated infections of bats might confer significant immunological memory and reduced susceptibility to rabies infection. Immune competence in bats can vary with body condition (via nutritional status and stress) and reproductive activity and, as a consequence, can lead to a lower rabies seroprevalence between or within bat species.

5. Intra and interspecific transmission of bat viruses

Bats are considered major hosts for alphacoronaviruses and betacoronaviruses and they play an important role as the gene source in the evolution of these two genera of coronavirus [53]. Most, if not all, alphacoronaviruses and betacoronaviruses found in mammals are evolutionally linked to ancestral bat coronaviruses [54]. Different species of *Rhinolophus* bats in China carry genetically diverse SARS-like coronaviruses, some of which are direct ancestors of SARS-CoV and hence have the potential to cause direct interspecies transmission to humans [54]. A large-scale study conducted worldwide on 282 bat species from 12 families demonstrated the presence of coronaviruses on 8.6% of bats whereas the ratio was only 0.2% on non-bat species [36]. A relationship between viral richness and bat species richness was demonstrated, suggesting that the diversity of bat CoVs has been driven primarily by host ecology [36, 41]. Preferred association between viral subclade and bat family was also observed. Bat-borne Dependoparvoviruses are also suspected to be the ancestral origin of adeno-associated virus (AAVs) in mammals [55]. Similarly, bats are the primary reservoir for 15 of 17 species of lyssaviruses [56]. Lyssaviruses may have evolved in bats long before the emergence of carnivoran rabies [6, 57].

Dissemination of viruses among bat populations is a complex system affected by many traits of the seasonal bats life. Seasonality and environmental conditions determine birthing periods, migrations, gregarious behavior, and torpor of each bat species. Each one may affect population density, rates of contact between individuals, and consequently the basic reproductive number of virus (R_0) and virus transmission between species. The basic reproductive number (R_0) is an important parameter in the dynamic of diseases and is the average number of new infections that would arise from a single infectious host introduced into a population of susceptible hosts [58]. Understanding how pathogens spread within their host populations is a key factor in epidemiology. It is especially difficult to study the vertical transmission of viruses in bats. Bats are very sensitive to disturbances and environmental changes, especially during breeding period. A disturbance in a maternity colony can produce an important mortality in newborn bats that may impact in the demography of population. The per capita transmission rate depends on the infectivity of the virus, the susceptibility of the host, but also on the contact

rate between susceptible hosts and infectious individuals. Social organization within the refuges thus plays a major role in virus transmission. Some bat species form a very large and tight monospecific or multispecific colonies of thousands individuals, e.g. the density of a hibernation colony of *Miniopterus schreibersii* near Barcelona was estimated at 1900 bats for square meter [58] (**Figure 4**). *Tadarida brasiliensis Mexicana* forms in Carlsbad Cavern (New Mexico), a colony with 793,838 bats [59]. This gregarious roosting behavior can provide large opportunities for viral exchange in bat colonies. Bat colonies are often composed by more than one species. Large colonies and multispecies associations are frequent among cave-dwelling bats, in particular during the maternity period. This colonial behavior confers thermodynamic and social advantages to reproductive females during pregnancy and lactation [60]. For instance, mixed colonies can be found in Southeastern Europe where *Miniopterus schreibersii*, *Myotis myotis*, and *Myotis capaccinii* are in direct physical contact. This cohabitation can facilitate virus transmission between species. The seroprevalence for EBLV-1 in *Myotis myotis* and *Miniopterus schreibersii* followed the same temporal pattern during 4 years [45], which could be explained by virus transmission between these two species. The size of the colony and species richness were two important ecological factors playing a major role in seroprevalence variability [45]. Virus transmission in colonies may follow different ways depending on the bat and virus species considered, i.e. aerosols, contact with feces, urine, blood, or other body fluids, or by bite. Ectoparasites should also be considered. There are almost no data on vertical transmission from mother to fetus. However, vertical transmission has nevertheless been reported. Transplacental transmission of Hendra virus (HeV) was shown in the fruit bat *Pteropus poliocephalus* [61]. Horizontal transmission is far more documented. Theoretical modeling of disease expansion has assumed large and well-mixed host populations. However, many wildlife systems have small groups with limited contacts among them. The distribution of seropositive bats against European Bat Lyssavirus type 1 (EBLV-1) is not random in bat colonies and follows a gregarious pattern, indicating a non-random transmission of viruses inside the colony. Most of gregarious species of bats have a metapopulation structure (consisting of periodically interacting, spatially discrete subpopulations) with variations in their subpopulations. The total number of individuals in the various subpopulations must be sufficient to maintain virus

Figure 4. Colony of *Miniopterus schreibersii* with individuals tightly close to each other.

circulation in the metapopulation over time, while immunity or death due to viral infection extinguishes transmission chains within individual subpopulations. In a longitudinal study in vampire bats of Peru, Blackwood et al. [62] found that persistence of rabies virus cannot occur in a single colony. Maintenance of rabies virus at levels consistent with field observations requires dispersal of bats between colonies, combined with a high frequency of immunizing non-lethal infections. The dynamic of virus infection in a bat colony usually produce periodic oscillations in the number of susceptible, immune and infected bats. The delay between the waves depends upon the rate of inflow of susceptible bats into the colonies as a consequence of new births, immigration of naïve animals from neighboring colonies, and expiration of immunity in previously infected animals. When a sufficient fraction of susceptible individuals in the bat population is reached, the virus spreads again if infected individuals joined the colony [63]. A high number of species might not only increase the rate of contact between bat groups and species but also could facilitate virus entry or spread through the higher mobility of individuals among colonies, especially if these bats exhibit a migratory behavior. The role of migratory species in virus dispersion is unfortunately poorly studied in spite of being very important.

6. Anthropization, human behavior, and dynamic of emergence

The main element for the emergence of an infectious disease is the contact. With no contact, there is no possibility for a virus to cross the species barrier. In the case of bat-borne diseases, a direct or indirect contact must occur for the disease to emerge and spread. Synanthropic bats are of course the first ones to be considered as a source of emerging viruses. However, they are far from being the only ones at risk for transmission to humans. It is not only the natural synanthropic behavior that matters but instead the whole complex of biology, ecology, behavior, landscape evolution, and anthropization.

The first interaction considered for transmission of bat-borne viruses to humans is hunting and consumption of bush meat [64]. This is a traditional interaction in which humans are potentially going towards bats and thus viruses. However, there is no documentation of direct origin of virus disease outbreak coming from bat hunting, butchering, and consumption. Bush meat has been for instance regularly considered for the emergence of Ebola [65]. However, there is no evidence of direct contact with bats and bats were not the primary bush meat. Bats might just be a reservoir involved in a sylvatic cycle involving other animals being the actual target of bush hunting. In places where bats are hunted and consumed such as Southeast Asia, there is no report of direct emergence of viral diseases coming from consumption or hunting. A more likely potential process of transfer of viruses from bats to humans might be the attractiveness of degraded environment for bats [41]. Indeed, a highest diversity of bat-borne viruses was demonstrated, as a consequence of a higher diversity of bats, in anthropized, degraded environments. Deforestation and anthropization, instead of leading to the elimination of bats as one would instinctively expect, generate conversely a higher diversity. This might be explained by the complexity of the anthropized environments, which offer opportunities to different groups

of ubiquity bat species, whereas natural environments might be more selective and suited for species with stricter ecological requirements. Anthropized environment displaying a higher biodiversity, the risk of virus transmission is therefore increased [41]. The impact of land use change on the emergence of diseases has been modeled to two main processes: (1) the perturbation hypothesis in which "land use change perturbs disease dynamics in multihost disease systems by disrupting the cross-species transmission rate" and (2) the pathogen pool hypothesis in which "land use change allows exposure of novel hosts to a rich pool of pathogen diversity, influencing the cross-species transmission rate" [66]. However, the same authors stated that these hypotheses tend to be vague or case specific with lack of theoretical foundation. This makes sense since the emergence of an infectious disease is an accidental process or in other words a very low probability event resulting from the sum of low probability independent events. According to this accidental process, an emergence cannot be predicted and will always appear as case specific. In the case of bats, numerous viruses have been found in bats but no direct transmission to humans has been formerly described. Emergence of bat-borne viruses is therefore most likely the consequence of the accidental association of a chain of events favored by structural elements from the human society. Although traced as a bat-borne virus, the coronavirus responsible for SARS seems to have been initially transmitted by civet meat to humans [31]. The outbreak itself was most likely triggered by human-to-human transmission through aerosols. The epidemic of SARS in 2003 was limited to hotels, high population density areas, and hospitals. No direct contact with bats was involved in the outbreak. Similarly, the MERS epidemic in the Arabic Peninsula was attributed to a coronavirus probably initially present in bats but transmitted to humans by dromedaries [34]. MERS was also involved, like SARS previously, in major nosocomial outbreaks [67]. In this case, also the trigger for the epidemic was not a direct contact with bats but the human society organization, close proximity with domestic animals, and nosocomial transmission.

The main risk for emergence of bat-borne diseases is directly linked to the development of anthropized environment and reduction of natural environments. It is often understood that deforestation and anthropization will lead to the disappearance of species. This is not always true and anthropized environments can provide an acceptable habitat for a large range of bat species, generating thus a higher diversity of bats and in turn of bat-borne viruses next to human dwellings. Anthropization generates a highly diverse environment in the vicinity of human, characterized by differing forest densities. Bats of differing ecology can find in anthropized environments niches compatible with their roosting and hunting needs. Natural environments are highly selective and compatible only with adapted species over a large surface, usually away from human settlements. In the exact contrary, anthropized environments provide a mosaic of ecosystems, very close to each other, each one corresponding to the needs of a given group of bat host. Insectivorous bats will find large populations of insects due to the presence of water, animals, and humans. Furthermore, house lights attract large number of insects at night. Houses and barns offer shelter for cave-dwelling bats while orchard and field can attract frugivorous bats. This environment is favorable to the occurrence of key parameters identified for virus transmission in large colonies of cave bats, i.e. shared roosting areas, close contact of different species, and regular introduction of infected individuals [45, 58]. However, in this specific environment, there is an additional aspect, the proximity of humans

and domestic animals. Another recent example is the first report of the presence of human and chicken blood in the diet of *Diphylla ecaudata* vampire bats living in the highly anthropized Caatinga dry forests of northeastern Brazil [68]. This attractive effect of anthropized environments on bats and the consequent promiscuity of bats, domestic animals, and humans are most likely to increase the risk of direct transmission of viruses and to the probability to trigger the accidental process of emergence.

7. Deforestation trends and increased risk of emergence

Bats have long rendered great services to mankind by acting positively on its environment and without living in a too close vicinity of human populations. However, by increasing the surface of cultivated areas and through the rapid growth of cities in the recent decades, men have drastically modified ecosystems which had remained in equilibrium for millennia. This evolution of ecosystems is even faster in Asia than in the rest of the world. Southeast Asia (SEA) is the region in the world that suffered the largest deforestation with a loss of 30% of forest surface over the last 40 years. In Thailand, agricultural lands represented 23% in 1960 and 40% since 1985 [69]. Similar trends were observed in other Southeast Asian countries [69]. In Cambodia, agricultural surfaces doubled from 15% in the 1980s to 30% in 2000. A similar trend was observed in Vietnam with an increase from 20% in 1990 to 35% today. In Indonesia, the growth was from 21% in the 1980s to 31.5% today. Deforestation is today linked to increased agricultural surfaces and to poorly managed urban growth. Owing to evolving land use, bat populations are setting in area closer to human dwellings [70]. Anthropized rural environments are characterized by a wide diversity of landscapes comprising houses, barns, fields, orchards, and woods of differing density. Human dwellings are also established close to water which along with the presence of animals is favorable for insects and insectivorous bats. Unlike natural environment which are highly selective, these altered landscapes are acceptable by a wide range of bat species, usually not encountered together, which establish close to human dwellings. This results in a higher density of bat-borne CoVs in the close vicinity of human dwellings [70–72], and thus a higher risk of human infection through direct contact or contamination by urine or feces. An aggravating factor is that the human population growth is higher in suburban and rural areas generating thus a higher pressure on land use, agricultural land, and deforestation with the most common activities being farming, logging, and hunting. The recent acceleration of deforestation in Southeast Asia and all predictions based on demographic burden on land use clearly indicate that the risk of contact and of transmission of new microorganisms which could turn pathogenic for humans will increase. It is thus just a matter of time, chance to encounter appropriated targets (human or animal in close contact with humans) and viral mutations to adapt to new hosts. Similar trends of deforestation are occurring in South America, but landscape organization is different, and the human population density is far lower than in SEA making thus the risk perhaps lower. If the exact time and nature of the emergence cannot be predicted, the increased probability of encounter and occurrence of emergence-leading chain of events yielded by anthropized environment must be considered seriously.

8. Prospectives

Bat-borne virus transmission is a complex issue associating at the same time viruses with a high potential for infectivity for humans and a lack of evidence of direct transmission from bats to humans. Hence, outbreaks have already occurred demonstrating the reality of this threat. An emergence cannot be predicted but some elements in the chain of events can and must be monitored, in particular: (1) the prevalence of the virus in wild species that inhabit the region; (2) the effects of environmental changes on the prevalence of pathogens in wild populations; and (3) the frequency of human and domestic animals contact with bats (including indirect contact with droppings, aerosols, saliva, or urine). The future of the viruses-bats-humans relationship seems to evolve in a dichotomic way: on one hand, the number of endangered bat species is growing and their natural habitat is decreasing. According to IUCN [73], 23% of bat species worldwide are considered to be decreasing. On the other hand, the increasing deforestation and extension of mosaic anthropized habitats will attract different bat species leading synanthropic behavior and contacts. The current mobility of people is unprecedented and is a very important epidemiological factor to consider, since it increases the risk of spreading diseases. Land modification, changes in vegetation patterns (deforested areas, new land crops), disturbances in vector and host species dynamics, and microclimate changes are most likely to increase the contact between human or livestock and wildlife [41, 74]. Monitoring bat-borne diseases and more importantly the environmental conditions bringing bats, viruses, and humans into contact will be crucial and should lead to the development of scenarios of risk management.

Conflict of interest

The authors declare the absence of any conflict of interest.

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