



*Edited by Lin-Fa Wang and Christopher Cowled*

# BATS AND VIRUSES

A New Frontier of Emerging Infectious Diseases

WILEY Blackwell



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## A New Frontier of Emerging Infectious Diseases

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*Edited by*

Lin-Fa Wang  
and  
Christopher Cowled

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# PREFACE

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The global burden of human suffering caused by infectious diseases has been lessened in the modern era by medical and technological advancements, yet the social costs of contemporary epidemics can still be devastating, and the economic costs can be orders of magnitude more severe than in the past. Modern communications have the ability to spread fear and panic to millions, while international air transport means the potential for infectious agents to move around the world within hours is a confronting reality. Globalization has connected countries and continents together in ways that make the impacts of emerging disease events in remote and distant places extend far beyond their geographic boundaries.

In the last two decades, some of the largest outbreaks of emerging infectious diseases, including the SARS virus outbreaks in 2003–2004, which caused an estimated more than \$50 billion damage to the world economy, and the Ebola virus disease outbreaks in West Africa started from 2014, which has claimed more than 10 000 lives to date, have implicated bats as their primary source. It is now thought that 75% of all emerging human infectious diseases originate in other animals, and bats are being increasingly recognized as one of the most important reservoirs for emerging viruses. In addition to SARS and Ebola viruses, bats are implicated as the source of diverse human pathogens, including *Nipah virus*, *Hendra virus*, *Marburgvirus*, the newly emerged MERS virus, and more. As the only flying mammal on earth, the unique biological features of bats distinguish them from all other mammals. Recent studies suggest that bats' ability to live longer and harbor a large number of viruses without displaying clinical diseases may in fact be related to the adaptation to flight.

It is more than a century since an association was first recognized between bats and a zoonotic virus (rabies virus); however, this area of research has been neglected to a large degree, as reflected by the fact that only one dedicated book has ever been published on this important topic, and that was in 1974. It was in this context of rapid progress in bat and virus research and the lack of a dedicated book in this area for the last four decades, that we felt it timely to embark on the goal of publishing a dedicated volume summarizing the recent progress and state of play with regard to research into bats and their viruses. Our endeavor was greatly helped by the enthusiasm of the invited chapter authors, many of whom are recognized leaders in their fields. We would like to take this opportunity to formally thank all of the authors for their dedication and professionalism. We also wish to thank the staff at John Wiley & Sons, especially Mindy Okura-Marszycki and Stephanie Dollan, for strongly supporting our project from its inception through to final production.

In this volume, we have tried to put equal emphasis on both pathogen and host biology. While research in some areas, such as the physiology and biomechanics of bat

flight and echolocation, have a long history and are quite advanced, others, including bat genomics and immunology are still in their infancy and a lot more work needs to be done before one can present a complete picture. On the other hand, with recent advances in next generation sequencing, the characterization of bat viruses and/or viral genomic sequences have undergone exponential growth, as evident from the detailed descriptions of major bat-borne virus groups in the dedicated individual chapters. While such advances are exciting and represent great progress, many significant challenges remain, including but not limited to:

1. *Isolation of live virus from bat specimens.* With the rapid accumulation of viral sequences from metagenomics studies, the success rate of virus isolation still remains extremely low. The true association of some of these viral sequences with bats is yet to be proven, and it is not always clear what role bats play in the viral replication cycle. The need to understand the emergence of new human pathogens from wild reservoirs builds a strong case for the proper biological characterisation of both viruses and their natural hosts.
2. *The species-specific nature of the current bat research.* With over 1200 species of bats described, extreme caution needs to be placed on generalizing findings made from a limited number of bat species. It is important to recognize that it will be extremely difficult, if not impossible, to make any pan-bat claim from the current early studies on bats and their viruses.
3. *Cross-species comparative studies.* In addressing the question “Are bats special?” in their ability to coevolve with viruses, there is a need for in-depth comparative studies with other mammalian species, especially mouse and human. However, due to the lack of proper reagents (especially antibodies), cell lines, and bat colonies, the studies presented in this book can only be considered preliminary and much more work is required in future.
4. *Virus-centric focus.* Although there have been a few recent publications on bat-borne bacteria and parasites, the data are very limited in comparison to the large volume of virus-related publications. For this reason, we have limited the discussion of this book to viral pathogens; however we hope to include other pathogens in future edition(s).

Finally, as the field is moving forward very rapidly, we tried our best to capture the latest findings and knowledge at the time of publishing. However, with the book project spanning more than a year, it is inevitable that some of the most recent advances may have been overlooked or occurred too late for inclusion. With the pace of discovery accelerating, we look forward to a new era of research on bats and their viruses, which in 2015 looks promising indeed.

LIN-FA WANG AND CHRISTOPHER COWLED  
April 2015

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# THE UNIQUENESS OF BATS

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## 1.1 INTRODUCTION

The aim of this chapter is to provide an overview of the distinctive features of bats, many of which are unique among mammals, and in particular to highlight features of their biology that may have some bearing on the high prevalence of viruses in this group (Luis *et al.*, 2013).

Bats are the only mammals with the capacity for powered flight. The associated skeletal adaptations of elongated forelimb bones were fully developed in the first fossil bat *Icaronycteris index* 50 million years ago, discovered in the Green River formation in Wyoming, USA (Jepsen, 1966, 1970). Also evident were auditory bullae at the base of the cranium, indicating the presence of large cochlea, associated with echolocation, which enabled bats to fly in darkness. Flight and echolocation allowed bats to occupy and eventually dominate the nocturnal aerial feeding niche where they are relatively free of competitors and predators. Among the exceptions are caprimulgid birds (nightjars and goatsuckers), an Old World bat hawk and a New World bat falcon. Owls cannot match the flight agility of bats, although they are opportunist predators at roosts (Fenton & Fleming, 1976).

From the same Eocene fossil beds in Wyoming, Simmons *et al.* (2008) described *Onychonycteris finneyi*, of similar age to *Icaronycteris index* but more primitive, in that its limb bones are intermediate in proportion between terrestrial mammals and other Eocene bats. The cochlea is also smaller indicating that echolocation was either less well developed or absent, supporting the view that flight evolved before echolocation. However, in the absence of a more extensive fossil record, the evolutionary history of bats from a small terrestrial shrew-like early mammal of the Triassic to the fossil bats found 150 million years later is a matter of speculation. The most plausible hypothesis is that bats evolved from a species similar to modern day tree shrews, in which the limbs and digits became connected by folds of skin and the forelimbs became elongated to form an aerofoil (Smith, 1977; Hill & Smith, 1984). Jumping from branch to branch led to gliding and eventually to flapping flight.

With 1301–1331 species (January 2014, N.B Simmons, Pers. Comm.; Simmons, 2015) bats are the second largest order of mammals, and the number of species continues to rise as new ones are described or the taxonomy of particular genera is reviewed. Nevertheless, bats continue to account for about a fifth of all mammals because the same processes are happening in the largest order of mammals, the rodents, which has about twice as many species as bats. Bats are distributed throughout the world, with the exception of some isolated oceanic islands such as Tahiti and the polar regions, although they breed inside the Arctic Circle (Rydell, 1989). However, although there are twice as many bat species in the Old as in the New World, bats achieve their greatest species richness in South America (Hutson *et al.*, 2001; Jones *et al.*, 2009). Regardless of continent or scale, latitudinal gradients of richness are qualitatively similar and species number increases with decreasing latitude and decreases with increasing elevation (Willig *et al.*, 2003). Family-level species richness varies greatly, from one and two species in the Craseonycteridae and Myzopodidae respectively to more than 300 species in the Vespertilionidae (Simmons & Conway, 2003).

Historically, bats were divided into two suborders: the Megachiroptera consisted of a single family, the Pteropodidae – Old World vegetarians with large eyes, which do not echolocate; and the Microchiroptera with 16 families of echolocating and mainly insectivorous bats. Recent phylogenetic analysis has revised the classification of bats, and two new suborders have replaced the old: The Yinpterochiroptera consisting of the Pteropodidae and five other families grouped within the superfamily Rhinolophoidea; and the Yangochiroptera, with three superfamilies – the Emballonuroidea, the Vespertilionoidea and the Noctilionoidea, comprising a total of 13 families (Teeling *et al.*, 2005).

## 1.2 FLIGHT

The ability to glide by extending flaps of skin between the limbs has evolved several times among mammals, in the marsupial sugar gliders and flying phalangers of Australia and New Guinea, in placental mammals like flying squirrels and colugos of Asia, and anomalures of Africa. Bats are unique, however, in their capacity for powered flight. All forelimb bones in bats are elongated, although the ulna no longer extends to the wrist and is vestigial, so pronation and supination (turning about the elbow) is no longer possible nor desirable. Digit one – the thumb – is free and clawed and is important for climbing and grooming, and in some cases for aggression. Digits two and three are

generally close together and form the rigid leading edge of the aerofoil. Digits four and five support the wing membrane or patagium, which consists of a double layer of skin, well provided with elastic tissue so that it can change shape in flight but retracts and folds at rest. The hind limbs are also elongated, attached to the patagium and involved in steering. They are generally joined to the tail by the interfemoral membrane which is sometimes used in prey capture. The overall flexibility of the wing means that some bats have a unique flying attribute – the ability to carry out stall turns – to rotate through 90° in their own body length.

In contrast to birds, where most power for flight comes from two muscles – the pectoralis and the supracoracoideus working antagonistically – flight in bats is powered by nine pairs of muscles, mainly abductors and adductors, concentrated towards the midline (in contrast to the situation in terrestrial mammals where the flexors and extensors of the limbs power locomotion). In birds the muscles that elevate and depress the wings are on the ventral surface, whereas in bats the elevators are dorsal and the depressors are ventral. The keel on the sternum of bats is much less prominent than in birds. The muscles responsible for opening and closing the wing are also situated in the proximal parts of the forelimb and their power is transmitted by extended tendons. The wing opens and closes in one plane and twisting is eliminated. The clavicle braces the shoulder joint against the axial skeleton, in contrast to the situation in birds where the coracoid provides a more rigid brace.

Although the hind limbs may be elongated, the pelvic girdle is reduced compared with the pectoral girdle, and the diameter of the birth canal is reduced. However, across the pubic symphysis, the interpubic ligament joins the pubic bones ventrally, and can expand to increase the diameter of the birth canal from 2 to 35 mm in *Tadarida brasiliensis*. This expansion is under the influence of the hormone relaxin (Crelin, 1969). The hind limbs have become rotated by 90° in many bats, although they have retained the ability for terrestrial locomotion, sometimes impressively so (Lawrence, 1969; Riskin *et al.*, 2006). In some groups, however, such as horseshoe bats (family Rhinolophidae), the limbs have rotated through 180° and terrestrial locomotion is no longer possible so they can only hang or fly, although some species are able to land on the ground in pursuit of prey and lift off from a stationary position.

The overall shape of the wing is an important determinant of flight capability and foraging behaviour. Wing loading refers to the weight of the bat divided by the total area of the flight membrane, so that high wing loading occurs in a large bat with relatively small wings. Aspect ratio is the square of the wingspan divided by the wing area and is low in bats with short broad wings and high in bats with long narrow ones. A principal components analysis between increasing wing loading and aspect ratio reveals four broad flight capabilities (Norberg & Rayner, 1987):

1. Slow open-air flight, long distance migration.
2. Slow maneuverable flight in cluttered environments.
3. Fast flight in cluttered environments.
4. Fast open-air hawking, short range migration.

Of particular relevance in the context of disease transmission is the migratory ability of bats which will be considered later. In addition, O'Shea *et al.* (2014) have

hypothesized that bat flight provides the selection pressure for co-existence with viruses through a daily cycle of activity that elevates metabolism and body temperature analogous to the febrile response in other mammals.

### 1.3 ECHOLOCAION

Although the role of the ears in enabling bats to avoid obstacles in the dark was established in the late 18th century by Spallanzani and Jurine, it was not until the mid-20th century that the use of echolocation to catch insects was revealed by Griffin and colleagues (Griffin, 1958). Echolocation involves the analysis by an animal of the echoes of its own emitted sound to gain information about its environment. Echolocation is used by most bats to detect obstacles and prey. It has also evolved in some nocturnal cave-nesting birds like swiftlets (*Collocalia*) of the Old World tropics and the South American oilbird (*Steatornis*) and among mammals in toothed whales and in some insectivores (Sales & Pye, 1974). It has, however, been best studied in bats where it has reached extraordinary levels of sophistication (Fenton, 2013).

Most bats produce their echolocation calls in the larynx, which in bats is proportionally larger, and is tensioned by well-developed cricothyroid muscles. Lips, flaps of skin and noseleaves appear to act as acoustic lenses, focussing outgoing signals. The external ears are generally large and have a cartilaginous projection or tragus at their base which may limit the receptive field to an area 30–40° either side of the midline and this may in turn affect the directionality of incoming echoes (Altringham, 2011).

Bats use a variety of echolocation calls with different combinations of signal strength, signal duration and pattern of frequency change over time. As they approach targets, they produce shorter and shorter signals to ensure the outgoing pulses do not mask returning echoes.

Echolocation calls are generally beyond the range of human hearing (and so by definition are ultrasonic) and in the frequency range 20–120 kHz. They are also of high intensity and loud enough to be uncomfortable if we could hear them. To avoid deafening themselves by their own emitted sounds, most echolocating bats separate pulse and echo in time. Furthermore, they disconnect one of the middle ear bones, the stapes, from the oval window at the entrance to the cochlea, by contracting the stapedius muscle. When foraging, bats emit pulses of ultrasound and the pulse repetition rate increases when the echoes indicate the presence of a prey item, in some cases up to 200 Hz. The stapedius muscle can operate at this frequency, one of the highest recorded in mammals (Altringham, 2011).

Horseshoe bats (Rhinolophidae), leaf-nosed bats (Phyllostomidae), and three species of moustached bats (Mormoopidae), separate pulse and echo in frequency. They do so by exploiting Doppler shifts of their outgoing signals, which are dominated by a single frequency.

High frequency sounds attenuate rapidly in air so that a bat echolocating with signals that have most energy at 30 kHz is unlikely to detect insect-sized targets beyond 40m. The frequency of sound is inversely proportional to its wavelength and so the higher the frequency the smaller the wavelength. The best sound for detecting an object is one with a wavelength similar in length to the object, so that bats feeding on small insects tend to use high frequency short wavelength calls.

Bats emit echolocation calls in pulses either at a constant frequency (CF) or frequency modulated (FM) or a mixture of the two. FM pulses are short, typically 2–5 ms long and sometimes less than 0.2 ms. If pulses were longer, the bat would be listening to the echo before it had finished emitting the pulse and neural mechanisms of echo interpretation require that to be avoided (Altringham, 2011). According to the autocorrelation function proposed by Simmons (1971), a bat behaves as if it stored the emitted pulse (in the inferior colliculus of the midbrain) and cross-correlates it with the returning echo (Altringham, 2011).

CF calls are typically 10–50 ms in duration and often have an FM component at the end. Many species with long CF components to their calls use an auditory processing system that is tolerant of pulse-echo overlap. This is possible because bats in the families Hipposideridae and Rhinolophidae have an acoustic fovea – a region of the cochlea that is extremely sensitive to the echo frequency of their calls – so that pulse and echo are separated in frequency rather than in time (Neuweiler, 1990; Altringham, 2011).

The Pteropodidae is the only family of bats not to have evolved laryngeal echolocation and relies on sight for orientation, together with olfaction for finding food. However, one genus within the Pteropodidae, *Rousettus*, has evolved a system of echolocation by rapid tongue clicking (Holland *et al.*, 2004), and as a result can roost deep in caves. Other members of the family may also roost in caves but only within sight of the entrance.

## 1.4 COMMUNICATION

In addition to its role in avoidance of obstacles and detection of prey, the sounds produced by bats are also important in communication between individuals (Altringham & Fenton, 2003). Although echolocation calls may have a communication function (Möhres, 1966; Barclay, 1982), social calls have been identified which often have a lower frequency than echolocation calls and may be audible to the human ear. Examples are distress calls (Russ *et al.*, 1998), mating calls (Lundberg & Gerrell, 1986), copulation calls (Thomas *et al.*, 1979), isolation calls when young are separated from their mothers (de Fanis & Jones 1995) and, together with their scent and the spatial memory of the mothers, enable young to be located among many millions on the wall of cave roosts (Balcombe & McCracken, 1992).

## 1.5 FORAGING, DIET, AND ECOSYSTEM SERVICES

Although bats have evolved a wide range of diets, they have retained a relatively simple digestive system and a relatively short intestinal passage time (Tedman & Hall, 1985). The majority of bat species are insectivorous, catching their prey in free flight or in various degrees of clutter, or gleaning, in which insects are taken from substrates such as leaves, bark or the ground. Such gleaners often have particularly acute hearing (Coles *et al.*, 1989) and can detect their prey by listening to the sounds of shimmering wings, or rustling, as the insect moves (Anderson & Racey, 1981; Swift & Racey, 2002). The majority of nocturnal moths, and also green lacewings, have evolved hearing organs that detect the bats' ultrasound and enable them to take avoiding action. Some arctiid moths

have evolved organs which generate sound that cause approaching bats to abandon their attack (Jones & Rydell, 2003).

Bats in the family Pteropodidae have large eyes and good night vision and feed on fruit, flowers, nectar, pollen, and leaves. Fruit contains little or no protein but bats can extract protein from pollen and leaves (Kunz & Ingalls, 1994; Long & Racey, 2007). The New World family Phyllostomidae includes many species with a diet of fruit, nectar and pollen which also catch insects to satisfy their protein requirements. The extent to which these bats rely on echolocation when feeding on plant products is unclear. However, some New World flowers have evolved nectar guides which reflect ultrasound to attract bats and encourage their role in pollination (von Helversen & von Helversen, 1999, 2003). Although the majority of bat species are insectivorous, some have become carnivorous, taking small mammals, reptiles and amphibians from the ground (Patterson *et al.*, 2003). Even more specialized are the piscivores, which echolocate ripples on the water surface before lowering their often enlarged feet into the water to gaff small fish (Schnitzler *et al.*, 1994). Vampire bats are unique as the only mammals to subsist entirely on a diet of blood. An anticoagulant in their saliva maintains blood flow once an incision has been made by sharp incisor teeth (Hawkey, 1966; Fernandez, 1999).

At least one species of vampire bat has an infrared detector on the nose leaf to assist in the localisation of prey, which in the case of the common vampire bat *Desmodus rotundus* is commonly cattle (Kürten *et al.*, 1984). Quadripedal locomotion is also well developed in vampires, which alight on the ground near their prey and are adept at avoiding their moving hoofs. They climb up the leg to the neck, make an incision and feed by lapping the blood. Before they can fly, they must lose weight and the kidney switches to water-eliminating mode. Once back in the roost, they must digest blood with no access to drinking water, so the kidney switches to a water conserving mode more efficient than that of some desert rodents (McFarland & Wimsatt, 1965). Cattle are not, however, debilitated by the loss of blood but by the diseases transmitted by the bats, the most serious of which is rabies (see Chapter 3).

As knowledge of bat diets becomes more detailed, so does awareness of the ecosystem services they provide (Boyles *et al.*, 2011; Kunz *et al.*, 2011). By analyzing feces, the proportion of insect pests in the diet can be determined and a monetary value placed on a colony of many millions of free-tailed bats *Tadarida brasiliensis* roosting in caves in Texas, not just in reduction of crops lost to pests but also in reducing the number of pesticide treatments the crop requires (Cleveland *et al.*, 2006). Similar ecosystem services are provided by wrinkle-lipped free-tailed bats, which act as a potential biological pest control agent through eating rice crops in Asia (Leelapaibul *et al.*, 2005). Wherever large colonies of bats roost, their guano is harvested as a fertilizer rich in nitrogen and phosphates. In many countries in the developing world, this is often the preferred fertilizer, because farmers consider that, unlike chemical fertilizers, it improves soil quality.

Fruit-eating bats disperse seeds over long distances and play an important role in forest regeneration (Lobova *et al.*, 2009; Fleming & Kress, 2013). Some plant-eating bats have become adapted to a diet of pollen and nectar and pollinate high value commercial crops such as durian in Asia (Bumrungsri *et al.*, 2009) or commonly used vegetables such as stink bean or petai (Bumrungsri *et al.*, 2008) as well as charismatic plants, such as baobabs in Africa and Madagascar (Baum, 1995; Andriafidison *et al.*, 2006).



## 1.6 HETEROTHERMY, DAILY TORPOR, AND HIBERNATION

The adaptation that has enabled insectivorous bats to colonize the north and south temperate zones is the capacity for heterothermy, in which body temperature is allowed to fall, sometimes close to ambient, from which it spontaneously rewarms. This is not an intermediate state between cold-blooded vertebrates or ectotherms and warm blooded vertebrates or endotherms but is a specialised form of homeothermy. Many temperate-zone bat species make use of daily torpor, allowing their body temperature to fall to save the energy increment that would be required to maintain a high constant body temperature or homeothermic state. In late summer, bats begin to accumulate body fat and as aerial insect density and ambient temperatures decline in autumn, the periods of daily torpor become longer and then continuous for days or weeks as the bat is hibernating. Hibernation is interrupted by spontaneous arousals, the frequency of which is related to ambient conditions. At latitudes where ambient temperatures are below freezing for long periods, arousals are less frequent than at 53°N in the UK, where over a 3-year period, pipistrelle bats *Pipistrellus pipistrellus* flew in every winter month and on a third of all winter nights (Avery, 1985). Bats will often fly when the winter temperature rises above the threshold for insect flight and winter feeding is often recorded although increases in body weight have yet to be established (Ransome, 2008). There may be other drivers of winter arousals such as the need to urinate, to drink or to check on ambient conditions, and perhaps reposition within the hibernaculum. Arousal from deep hibernation, in which the bat's body temperature is close to ambient, is energetically expensive in the amount of fat metabolized. That explains the mass winter mortality, of over six million bats of several species in North America, attributed to the cold-adapted fungus *Pseudogymnoascus destructans*. This invades the skin of the muzzle, forearm, and wing membranes, penetrating the epidermis and dermis and causing the bat to arouse repeatedly during hibernation. More fat is metabolised in doing so than will last the bat for the duration of winter and the bat starves to death (Reeder & Moore, 2013).

Although many groups of mammals (such as some carnivores and Eulipotyphla) and some birds (such as humming birds) make use of torpor, bats have taken the adaptation to extremes during pregnancy and lactation. If pregnant bats experience periods of inclement weather, so that their insect food is no longer flying, they will become torpid and the development of the fetus will be slowed or halted. Conversely, if they experience high ambient temperatures and abundant food during pregnancy, foetal development will accelerate (Racey, 1973a; Racey & Swift, 1981). Among mammals in general, the gestation period is fixed by the foetal genotype and is resistant to alteration by environmental factors (Racey, 1981). The fact that foetal development in bats may be slowed, stopped or accelerated depending on ambient temperature and food supply is unique among mammals and may be related to the fact that they have one of the slowest recorded rates of foetal growth (Racey, 1973a, 1981).

The timing of the reproductive cycle of male bats of the temperate zone is also influenced by changes in ambient temperature and food supply. Premature arousal of captive pipistrelle bats *Pipistrellus pipistrellus* from hibernation with an abundant food supply results in the initiation of spermatogenesis. Conversely, spermatogenesis is delayed in captive noctule bats *Nyctalus noctula* in which hibernation is prolonged by several months (Racey, 1971).