Emerging infectious diseases (EIDs) are defined as infections that have newly appeared in a population or have undergone a rapid change in incidence or geographic location. Since the 1940s, more than 300 EIDs have been recorded, most of which are viruses. Approximately 75% of human EIDs originated from animals. Of all the EIDs, zoonoses from wildlife represent the most significant threat to human health. Zoonotic EIDs have been identified in a variety of wildlife animals, including ungulates, carnivores, rodents, primates, bats and other mammal and non-mammal species. AIDS, the most significant EID of modern times, originated from non-human primates. Rodents have long been recognised as an important source of EIDs including hantavirus, plague and lyme disease. In the last few decades, bats (Order Chiroptera) have received growing attention as reservoirs for EIDs. Particularly, a number of high-profile zoonotic viruses with significant human and animal morbidity and mortality have been linked to bat reservoirs.

Although it is unclear whether bats are special in their ability to harbour a variety of highly virulent viruses, several reviews suggest that certain unique biological and behavioural characteristics of bats may be responsible for their seemingly “super” ability to peacefully co-exist with different viruses. These include the ability for long-distance dispersal through flight, change of body temperature through the process of torpor (daily change) or hibernation (seasonal change), long lifespan, echolocation, high population density and unusual social behaviours and population structure.

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Newly emergent zoonotic diseases of bat origin

Almost a century ago, bats were identified as carriers of the rabies virus in South and Central America. In recent times, related viruses in the genus Lyssavirus of family Rabdoviridae have been identified in bats of different species around the world, such as the Australian bat lyssavirus. Although the discovery of novel bat lyssaviruses contributes to the recognition of bats as an important reservoir of viral zoonoses, it was the identification of the following totally new bat zoonotic viruses that raised the profile of bats to an unprecedented new level.

Paramyxoviruses

Although there had been some description of bat paramyxoviruses in the past, it was the emergence of Hendra virus outbreak in Australia in 1994 that heralded the beginning of a surge in association of bat paramyxoviruses with severe zoonotic diseases. Hendra virus was the first biosafety level 4 (BSL4) agent identified in the paramyxovirus family. Infection of humans by Hendra virus has only been detected via transmission from horses and there is no evidence of direct bat-to-human transmission. Since the first discovery of Hendra virus, there have been more than 36 independent, spillover events, responsible for the death of four out of seven humans infected with the virus and more than 70 horses. For unknown reasons, 2011 witnessed 18

Figure 1. A colony of black flying foxes (Pteropus alecto) in Queensland, Australia. The insert shows a black flying fox resting on a table in the animal facility at the CSIRO Australian Animal Health Laboratory in Geelong, Australia. Photos courtesy of Gary Crameri and Susan Wilson.
separate Hendra virus outbreaks in horses with wider geographic locations than previous years and the infection of a domestic dog, most likely from sick horses on the same property⁶.

Nipah virus, closely related to Hendra virus, first emerged in Malaysia in 1998–99, as a result of suspected multiple bat-to-pig spillover events⁸. This was followed by a massive pig-to-pig transmission, which then led to pig-to-human transmission. The outbreaks claimed more than 100 human lives in Malaysia and Singapore; nearly all were believed to be infected from direct contact with infected pigs. Since 2001, a different strain of the Nipah virus emerged in India and Bangladesh, causing outbreaks in humans with a mortality of up to 90%. This strain of Nipah virus is capable of direct bat-to-human and human-to-human transmission, and is continuing to cause outbreaks almost on an annual basis¹⁰. It is not clear whether the difference in transmission of the two Nipah virus strains is mainly due to virological difference or other social and behaviour differences, although a recent comparative study in the ferret model suggests that viral factors are at least partially responsible for the observed differences in transmission¹¹.

Menangle virus, tentatively classified in the genus Rubulavirus within the family Paramyxoviridae, was responsible for an outbreak of reproductive disease outbreak in a large commercial piggery in New South Wales, causing reduced farrowing rates and stillbirths with deformities in pigs¹². Two abattoir workers, who were in close contact with infected pigs and suffered an influenza-like illness, had high levels of convalescent neutralising antibodies to Menangle virus. Neutralising antibodies against Menangle virus can be detected in all four species of Australian flying foxes, the black flying fox (Pteropus alecto), grey-headed flying fox (P. conspicillatus) and the little red flying fox (P. scapulatus). A variant of Menangle virus with 93% overall nucleotide sequence identity was recently isolated from urine samples of the black flying fox²⁰. A highly related virus, Tioman virus, was isolated from a Malaysian flying fox Pteropus hypomelanus²¹. The potential of Tioman virus to infect and cause disease in humans or other animals is unknown. However, experimental studies indicated that pigs are susceptible to infection by Tioman virus and there is serological evidence for infection of humans on the Tioman Island in Malaysia where the virus was first isolated²¹.

Finally, it is worth noting that an extensive surveillance study conducted worldwide with 119 bat and rodent species (9,278 individuals) revealed 66 new paramyxoviruses⁶. Hypothesis tests in a maximum likelihood framework permit the phylogenetic placement of bats as tentative hosts at ancestral nodes to all modern paramyxoviruses, further highlighting the importance of bats as an important source of potential future zoonotic paramyxovirus outbreaks¹⁶.

Filoviruses

Filoviruses, represented by Ebola and Marburg viruses, represent the most deadly viruses known to infect humans. After many decades of hunting, it was revealed in 2005 that bats of at least three different species in Africa were serologically positive for Ebola virus and contained Ebola virus RNA¹⁷. Similar studies demonstrated bats are also the likely reservoir host of Marburg virus. Live filoviruses have since been isolated from bats in Africa. Serological surveillance suggested that Ebola, Marburg and/or other related filoviruses are also present in bats in Asia, with Ebola Reston virus-specific antibodies detected in bats in the Philippines⁶. Although Ebola Reston is considered to be non-pathogenic to humans, the recent introduction of the virus into the domestic pig population raises the possibility that the host-switching of the virus may eventually lead to pathogenesis in humans¹⁹. A recent study also indicated the presence of an Ebola-like virus in microbats in Spain²⁰, although its pathogenic potential in humans is yet to be determined. So the full genetic diversity and geographic distribution of filoviruses in bats is yet to be determined, and it is important that the international community remains vigilant in global surveillance to minimise the impact of potential future outbreaks of novel filoviruses from bats.

Coronaviruses

The severe acute respiratory syndrome (SARS) is the first human pandemic outbreak of the 21st century caused by a previously unknown virus, the SARS coronavirus²¹. Conservative estimation of global economic loss due to SARS is at least US$50 million. Although SARS virus was detected in several animal species, including the palm civet, in a wet market in Southern China during the 2003 outbreaks, none of these animals could be confirmed as the natural reservoir host due to the lack of widespread and persistent infection in their populations. Instead, serological and molecular data revealed that highly related viruses or SARS-like coronaviruses were present in horseshoe bats in the genus Rhinolophus, strongly suggesting that bats are the natural reservoir hosts of SARS coronavirus²². It is hypothesised that the progenitor virus, which led to the mass SARS outbreaks, originated from bats of a yet to be identified species and transmitted to humans through one or more intermediate hosts, which act as both an adaptation and
amplification host\(^2\). Since 2005, numerous reported studies discovered a large number of coronaviruses in bats, including SARS-like coronaviruses from different parts of the world. These findings led to the hypothesis that bats are probably the hosts of all ancestor coronavirus lineages from which modern coronaviruses of different mammalian hosts were derived\(^2\), just as the case for paramyxoviruses discussed above\(^3\).

**Reoviruses**

Reoviruses or respiratory, enteric orphan viruses were first discovered in the early 1950s and have never been associated with any severe and acute disease in humans, and hence the name orphan virus. In 2006, the first bat-borne zoonotic reovirus, named Melaka virus, was discovered during an investigation of a severe flu-like illness in a patient in Melaka, Malaysia\(^2\). Epidemiological studies later revealed that the virus was also responsible for the illness of the patient’s two children, indicating a human-to-human transmission followed by the initial bat-to-human transmission. Melaka virus is closely related, in molecular sequence and serological cross-reactivity, to two bat reoviruses previously isolated in Australia and Malaysia. A retrospective serological study revealed that 13% of human volunteers from Tioman Island of Malaysia were seropositive to this group of viruses, suggesting that bat orthoreoviruses may infect humans more frequently than reported. Indeed, since the first report of Melaka virus outbreak in 2006, at least five independent severe respiratory disease events in Malaysia and Hong Kong have been linked to infection of this group of bat reoviruses, now collectively classified as pteropine orthoreoviruses\(^2\). A recent study identified three different reoviruses in European insectivorous bats, which belong to the species group mammalian orthoreovirus (MRV) and are substantially different from the Australasian pteropine orthoreoviruses\(^2\). Although MRVs are associated with rather mild and clinically unapparent infections in their hosts, there is growing evidence of their ability to also induce more severe illness in dogs and humans. These newly discovered bat reoviruses highlight the need to further investigate the potential of host switching and zoonotic potential of both known and unknown bat reoviruses.

### Table 1. Comparison of transmission mode and possible drivers for emergence.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Wildlife-human interface</th>
<th>Examples of putative drivers</th>
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<tr>
<td>Hendra virus</td>
<td>Indirect, bat to horse, then to human</td>
<td>Redistribution of bat population as a result of climate change</td>
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<td>Human population growth and urbanisation</td>
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<td>Starvation of bats due to natural disaster</td>
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<td>Nipah virus (Malaysia)</td>
<td>Indirect, bat to pig, then to human</td>
<td>Agricultural intensification (dual land use)</td>
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<td>Habitat destruction</td>
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<td></td>
<td></td>
<td>Climate change</td>
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<td>Nipah virus (Bangladesh)</td>
<td>Direct, consumption of juice contaminated with bat secretion</td>
<td>Unusual agriculture activities</td>
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<td>Cultural tradition and behaviours</td>
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<tr>
<td>Menangle virus</td>
<td>Indirect, bat to pig, then to human</td>
<td>Agricultural practices</td>
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<td></td>
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<td>Close proximity of piggery to bat colony</td>
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<tr>
<td>SARS-CoV</td>
<td>Indirect, bat to other wildlife animals (civet especially), then to human</td>
<td>Rapid economic growth in the region</td>
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<td>Desire for game meat</td>
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<td>Live wild animal trading in wet markets</td>
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<td>International travel</td>
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<td>Ebola virus</td>
<td>Indirect, bat to primate or game animals, then to human</td>
<td>Desire for game meat (bush meat)</td>
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<td>Live wild animal trading</td>
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<td>Indirect, bat to primate, then to human</td>
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<td>Melaka and related viruses</td>
<td>Direct, bat to human through bat secretion</td>
<td>Urbanisation</td>
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<td>Tourism</td>
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</tbody>
</table>
Other viruses

Although only those bat viruses with known zoonotic transmission are discussed in this brief review, it is important to emphasise that bats are increasingly recognised as host of a large number of other viruses, such as astroviruses and herpesviruses. Most importantly, influenza viruses and hantaviruses have also been detected in bats.

Interface with wildlife – a brief review of drivers for emergence

Climate change, intensive farming, habitat destruction, urbanisation and international travel are some of the well recognised drivers for emerging infectious diseases (EIDs), which is also true for the emergence of bat-borne zoonotic viruses. As summarised in Table 1, although most bat viruses entered the human population via an indirect transmission route, there are examples of direct bat-to-human transmission as well. It is important to differentiate the roles that intermediate hosts play in the emergence of bat zoonotic viruses. For example, the Hendra and Nipah virus isolates obtained from human cases were almost identical to those found in bats and horses or pigs. In other words, the intermediate hosts play a role of the amplifying host in raising the virus load to a level which is sufficient for transmission into human populations. On the other hand, civets played a dual role in both amplifying and adapting the SARS-CoV for transmission to humans. It is clear that even with the limited number of bat zoonotic viruses reviewed here, different drivers are responsible for the emergence. It is impossible to devise a one-for-all strategy to fight future bat zoonotic virus outbreaks.

Concluding remarks

Considering that there are over 1000 species of bats and they are present in almost every corner of the globe, it is almost certain that future outbreak of bat-borne zoonotic viruses will happen. The best way to prevent or mitigate the impact of such outbreaks will be to adopt a One Health approach by combining bat surveillance, public health education and basic research into bat biology, immunology and ecology in order to better understand bat-virus interaction and the triggers for spill over events.

References


Biography

Prof. Lin-Fa Wang is an OCE Science Leader and Senior Principal Research Scientist at the CSIRO Australian Animal Health Laboratory and the director of the Program in Emerging Infectious Diseases at Duke-NUS Graduate Medical School. His research interests are in emerging bat-borne viruses and host-pathogen interaction.