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Overview

An Overview of Animal Models for Arthropod-Borne Viruses

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Arthropod-borne viruses (arboviruses) have continued to emerge in recent years, posing a significant health threat to millions of people worldwide. The majority of arboviruses that are pathogenic to humans are transmitted by mosquitoes and ticks, but other types of arthropod vectors can also be involved in the transmission of these viruses. To alleviate the health burdens associated with arbovirus infections, it is necessary to focus today's research on disease control and therapeutic strategies. Animal models for arboviruses are valuable experimental tools that can shed light on the pathophysiology of infection and will enable the evaluation of future treatments and vaccine candidates. Ideally an animal model will closely mimic the disease manifestations observed in humans. In this review, we outline the currently available animal models for several viruses vectored by mosquitoes, ticks, and midges, for which there are no standardly available vaccines or therapeutics.

Abbreviations: arbovirus, arthropod-borne virus; CHIKV, Chikungunya virus; DENV, Dengue virus; TBEV, tick-borne encephalitis virus; ZIKV, Zika virus

In nature, arthropod-borne viruses (arboviruses) are transmitted between vertebrate hosts by hematophagous (blood-feeding) arthropod vectors, including mosquitoes and ticks. Before its transmission to a susceptible host, an arbovirus must first replicate to sufficient levels inside the arthropod vector. The virus then disseminates to the salivary glands of the vector, and the infectious saliva is injected into a host during the blood-feeding process. Thus, the maintenance of an arbovirus in nature involves a triad of interactions between the virus, the vertebrate host, and the arthropod vector. Mosquitoes, ticks, and midges are well-established vectors for transmission of many viruses that cause disease in humans. Over the past 20 y, there has been a significant increase in the number of human cases and in the geographic distribution of several arboviruses.[39] Every year, millions of people become infected with a mosquito-borne virus, and several thousand people are infected with a tick-borne virus. The emergence of various arboviruses can be attributed to several factors, including virus adaptation to new susceptible hosts, travel of persons between endemic and nonendemic regions, and climate changes that allow for greater worldwide distribution of vector species.[39]

To better understand and effectively control these viruses, it is necessary to establish appropriate animal models that demonstrate similar clinical manifestation and disease progression as seen in humans. However, there are many challenges in developing arbovirus animal models, given that many arboviruses do not readily cause lethal infection, nor do they approximate the pattern of human disease in standardly used laboratory animal species. In addition, the presence of saliva at the site of vector blood feeding enhances the infection of mosquito- and tick-borne viruses.[50,59] The role of arthropod saliva in disease progression makes evident the need to replicate the natural route of virus transmission in a laboratory setting, and it further complicates the development of suitable animal models. Here we examine currently available animal models for several viruses transmitted by mosquitoes, ticks, and midges, for which vaccines and therapeutics are not readily available or do not exist.

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Animal Models for Mosquito-borne Viruses

Dengue virus (DENV), Chikungunya virus (CHIKV), and Zika virus (ZIKV) have caused large outbreaks on multiple continents, and large portions of the world's population live in regions where there is a risk of DENV, CHIKV, or ZIKV transmission. Although there are numerous mosquito-borne viral diseases (Table 1), this section focuses on the currently available animal models for DENV, CHIKV, and ZIKV. The primary vector for each of these viruses is the *Aedes aegypti* mosquito. *A. albopictus* is also a competent vector for both DENV and CHIKV, whereas other vector species for ZIKV have yet to be identified.[21,44,63,69] Both *A. aegypti* and *A. albopictus* are dispersed throughout tropical and subtropical regions of the world. *A. albopictus* tolerates more temperate regions than *A. aegypti*, and *A. albopictus* has expanded further north into the Americas, Europe, and Asia.[34] As global climate changes continue, the regions for both of these species of mosquito might continue to expand.

Dengue virus. DENV is a member of the *Flaviviridae* family and has 4 serotypes (DENV 1 through 4). Clinical symptoms of DENV are rapid onset of fever, headache, arthralgia, abdominal pain, nausea, and rash. Although many cases are self-limiting, some

Table 1. Mosquito-borne viruses

Disease	Family	Vector	No. of infections annually	Mortality rate	Treatment	vaccine	Animal models available: Immuno-competent	Animal models available: Immuno-compromised	Humanized or zooized	Notes	References
Dengue virus (types 1–4)	Flaviviridae	*Aedes aegypti* (primary) and *A. albopictus*	284–528 million	1% to >20% depending on care	none	for people 9 to 45 y old in endemic areas	Mice (A/J), NHP	Mice (AG129, A129, Stat1, Stat2, MAVS)	SCID xenografted with human cells	Potential vaccines should be tetra-valent	11, 26, 72
Zika virus	Flaviviridae	*Aedes aegypti*	>25,000 in USA and territories; 0.5–1.5 million in Brazil	None reported, but rise in Guillain–Barré and micro-encephaly	none	none	Cynomolgus macaques, rhesus macaques	Mice (AG129; A129; IFNα/βR$^{+/-}$; IFNα/βR$^{-/-}$)	None	Other mosquito species being tested	17, 32, 48, 55
Yellow fever virus	Flaviviridae	*Aedes aegypti*	200,000	15% to 50%	none	available but not safe in some patients	Mice (CD1), hamsters, rhesus macaques	Mice (AG129)	None	AG129 mice can be used with vaccine strain of virus at ABSL2	58, 67
West Nile virus	Flaviviridae	*Culex* spp.	~2000 in USA	<1% non-neuro-invasive cases, ~10% for neuro-invasive	none	available for horses	Mice (C57Bl/6, Swiss–Webster), hamsters, zebra finches	None	None	Can cause disease in horses and birds (corvids)	2, 4, 25
Japanese encephalitis virus	Flaviviridae	*Culex* spp.	30,000–60,000	20% to 30%	none	available	Mice (C57Bl/6, Swiss), rhesus macaques	Mice (AG129)	None	≤50% of people develop neurologic sequelae	8, 49, 68
Rift Valley fever virus	Bunyaviridae	*Aedes*, *Anopheles*, *Coquillettidia*, *Culex*, *Eretmapodites*, and *Mansonia* spp.	Small out-breaks (~1 per year)	10% to 20%	support-ive care	for use in animals only	Mice (Balb/c), rats (Wistar–Furth, Lewis, Brown Norway), rhesus ma-caques	None	None	Causes disease with 10% to 20% mortality and high rates of abortion in ruminant animals	5, 54
Chikungunya virus	Togaviridae	*Aedes aegypti* (primary) and *A. albopictus*	110,000 (N and S America)	<1%	none	none	Mice (infant), hamsters, cyno-molgus macaques, rhesus macaques	Mice (IFNα/βR$^{+/-}$, IFNα/βR$^{-/-}$)	None	Hamsters do not exhibit clinical signs of illness but develop inflamm-atory lesions in joints and skeletal muscle	6, 12, 13, 36, 46

Table 1. Continued

Disease	Family	Vector	No. of infections annually	Mortality rate	Treatment	vaccine	Animal models available: Immunocompetent	Animal models available: Immunocompromised	Humanized or zooized	Notes	References
Venezuelan equine encephalitis virus	Togaviridae	*Aedes spp.* *Culex spp.*	Outbreak involving 75,000–100,000 people in Venezuela in 1995	< 1%	supportive care	for use in animals only	Mice (Balb/C and C3H/HeN) cyno-molgus macaques	Mice (SCID)	none		18, 29, 66
Eastern equine encephalitis virus	*Togaviridae*	*Culiseta melanura* in birds; *Aedes*, *Coquillettidia*, and *Culex* spp. transmit to humans	~6 human cases in N and S America per year	~33%	supportive care	none	Mice (Balb/c), golden hamsters, common marmosets	none	none	high incidence of lasting neurologic damage; many survivors develop sequelae	1, 10, 51

cases progress to dengue hemorrhagic fever or dengue shock syndrome. Natural hosts of DENV are mosquitoes, humans, and nonhuman primates. Numerous models using small animals have been developed with varying degrees of success (Table 1). Several commercially available strains of immunocompetent adult mice have been evaluated for susceptibility, including BALB/c, C57BL/6, A/J, and C3H/He. Most immunocompetent strains were not susceptible to DENV, with the exception of A/J mice, which had detectable viremia, transient thrombocytopenia, and developed paralysis.[26] The majority of DENV mouse models require humanized or immunosuppressed animals to develop clinical manifestations resembling human disease. SCID mice have been xenografted with a variety of human cells, including peripheral blood lymphocytes, liver cells, K562 cells, and hepatocarcinoma cells; after inoculation with DENV, many of these humanized mouse models displayed disease characteristics similar to human disease manifestations.[11,72] After DENV challenge, AG129 mice, which lack IFNα/β and IFNγ receptors, develop clinical symptoms similar to human infection and have a sustained antibody response.[11,72]

As a naturally occurring host, NHP can be used for DENV research as well. Although NHP do not have a clinical disease manifestation, they do demonstrate immune responses that are helpful for vaccine and pathogenesis research.[72]

Chikungunya virus. CHIKV is a member of the *Togaviridae* family. The name Chikungunya comes from the East African language of Makonde and means "that which bends up." This name refers to the incapacitating arthralgia that is characteristic of the disease and that lasts for several days or becomes a chronic condition. Additional symptoms include fever, headache, muscle pain, nausea, and rash. Mouse, hamster, and NHP models have been established for studying CHIKV disease pathophysiology and evaluation of therapeutic and vaccine candidates.[6,12,13,36,46] Immunocompetent adult mice are not susceptible to CHIKV, but neonatal C57BL/6 mice are susceptible to CHIKV infection.[13] In addition, adult IFNα/β receptor knockout mice, similar to those used for DENV research, can be used for models of mild or severe CHIKV infection, depending on the degree of the receptor deficiency. The results of these studies align with clinical manifestations in humans of comparable age and are useful for pathogenesis studies.[13] Unlike the established mouse models, golden hamsters do not exhibit clinical signs of illness after CHIKV infection. Despite this characteristic, there are benefits to using hamsters in CHIKV studies. First, the hamster model yields a sufficiently high viremia, enabling over 50% of mosquitoes to become infected after feeding on a CHIKV-infected hamster.[6] Furthermore, CHIKV-infected hamsters develop inflammatory lesions in joints and skeletal muscle, mimicking the disease in humans.[6] Studies using rhesus macaques (*Macaca mulatta*) and cynomolgus macaques (*M. fascicularis*) have demonstrated that not only do these animals develop an acute illness similar to human disease, they can be used to study the reproductive effects and age-associated changes in disease progression.[12,36,46]

Zika virus. Like DENV, ZIKV is a member of the *Flaviviridae* family. In 2012, it was determined that there were 2 distinct ZIKV lineages (African and Asian), and the Asian lineage has been responsible for the recent global expansion.[23] Typically ZIKV infection is asymptomatic or presents as a mild febrile illness with headache, muscle pain, and rash. A correlation between increases in microcephaly and neurologic disorders in infants and

Guillain–Barré syndrome in adults spurred the World Health Organization to declare a public health emergency in February 2016.[70] Several rodent models have been attempted, and it appears that, as needed to study DENV and CHIKV, mice deficient in IFN receptors are the most susceptible to ZIKV. Immunocompetent CD1 and C57BL/6 mice showed no evidence of susceptibility to ZIKV infection.[55] In comparison, A129 and AG129 mice showed disease manifestations and offer potential models for antiviral and vaccine testing.[55]

Further animal model development examining the reproductive effects of ZIKV used IFNAR1$^{-/-}$ dams crossed with wild-type male mice to produce IFNAR1$^{+/-}$ offspring. All dams were infected with ZIKV around gestational day 7 and fetuses were harvested 1 wk later. Many of the IFNAR1$^{+/-}$ offspring had been reabsorbed, and all others showed signs of intrauterine growth restriction.[48] Although these current models will be useful in the treatment and prevention of ZIKV, their immunocompromised status means that additional models are needed to evaluate pathogenesis. NHP models have successfully been developed using rhesus and cynomolgus macaques. For both species, clinical findings were limited to a rash at the site of injection in few animals and mild to moderate inappetence in some rhesus macaques. Viral titers have been detected in blood, urine, and saliva samples from both species, as well as in vaginal swabs taken from the rhesus macaques.[17,32] Reproductive effects are currently being evaluated in the rhesus model, and although complete results were not published at the time of this review, blood samples yielded detectable viral titers for several weeks longer taken in pregnant macaques infected during the first trimester than nonpregnant animals.[17] Because NHP are both immunocompetent and a naturally occurring host for ZIKV, these models may provide a more accurate translation to human cases than currently available mouse models.

Animal Models for Tick-borne Viruses

Unlike many mosquito-borne diseases, tick-borne viruses tend to have low species specificity. This characteristic reflects the natural feeding cycle of the tick: throughout its lifecycle, ticks may feed on different sizes or species of host, often with little regard to the host species. Humans are not a normal host for ticks, and human infection is inevitably the result of sylvatic escape. Due to their comparative host promiscuity, most tick-borne viruses lend themselves well to study in laboratory animals. The best-known tick-borne viruses come from 3 main viral families (Table 2): Flaviviridae, Bunyaviridae, and Thogotoviridae. A special case also exists for African swine fever virus, an asfivirus. This virus is not medically significant in humans but instead is agriculturally important. We include African swine fever virus in this review because the solution to the challenge posed by its unique species-specificity is illustrative of the scientific potential of 'zooized' mice. Like humanized mouse models, which have received human cells or tissues to better model diseases that infect humans, zooized mice have been implanted with cells or tissues from another species to provide an alternate option for species-specific pathogens.

Flaviviridae. The flaviviruses are a diverse group of enveloped viruses vectored both by ticks and mosquitoes. The tick-borne subgroup (group B) flaviviruses are led by the tick-borne encephalitis virus (TBEV). TBEV is actually a group of closely related virus subtypes found throughout Europe and northern Asia, including the European, Siberian, and Far-eastern subtypes. The primary model for this disease is immunocompetent mice, commonly BALB/c or C57BL/6, which develop signs of febrile and neuroinvasive illness when dosed intracerebrally or intraperitoneally with TBEV.[19,71] Primate models using African green monkeys (*Cercopithecus aethiops*) and cynomolgus macaques have been attempted but fail to produce signs of illness beyond mild fever.[53] There is some indication that dogs may be able to serve as a larger-animal model compared with mice, because dogs develop illness when infected naturally by ticks;[62] however, further studies are needed to examine the potential of such a model.

Alternatively, TBEV can be modeled using Langat virus, which is a close relative of TBEV but is unknown to produce human disease naturally. C57BL/6 mice injected subcutaneously with Langat virus develop febrile illness.[47] The disease manifestations and mortality of the virus can be enhanced by using immunocompromised Ccr5$^{-/-}$ or IPS1$^{-/-}$ mice.[35] In addition, infant rats have been used with Langat virus to model the effects of TBEV.[42]

BALB/c mice have been used to study Powassan virus, another group B flavivirus that can be thought of as a North American version of TBEV. Mice infected intradermally with greater than 10^3 pfu of Powassan virus quickly develop febrile and neuroinvasive illness that mirrors human Powassan encephalitis.[24,56] In addition, *Peromyscus* mice, one of the natural reservoirs of Powassan virus, may prove to be a useful research animal for modeling persistent resistance, given that these species are both available for and have been used in laboratory settings.[3]

Alkhumra hemorrhagic fever virus and Kyasanur Forest virus have been shown to infect BALB/c mice, with varying degrees of clinical outcomes between the 2 viruses.[57] Louping ill virus, an agriculturally important flavivirus of sheep, can be modeled in BALB/c mice and (albeit less reliably) in lambs.[60] As the natural host, adult laboratory sheep show promise for pathogenesis studies.

Bunyaviridae. Several bunyaviruses are transmitted by ticks. The most well-known of these is Crimean–Congo fever virus, a hemorrhagic disease. This virus has been studied in both STAT1$^{-/-}$ and IFNα/βR$^{-/-}$ mice for vaccine studies.[16,33] In addition, transmission studies have been accomplished by using infected infant mice as a source for tick infection and guinea pigs as a final host.[15]

Severe fever with thrombocytopenia syndrome virus has been tested in mice. Immunocompetent C57BL/6J mice have been used in immunization trials after being dosed intraperitoneally with 3×10^7 pfu of this virus; however, these mice cleared the virus and failed to develop severe symptoms.[40] Immunocompromised A129 mice infected with 10^6 ffu of the virus were shown to develop lethal illness, although the exact cause of the variable lethality was not clear.[61] A lethal infection can be produced by using IFNAR$^{-/-}$ transgenic mice.[65]

Heartland virus was recently described as a cause of human disease in the United States, and animal models are still under development. Rabbits have been shown to seroconvert without developing viremia or signs of infection.[22] Recently published studies indicate that, similar to many other arboviruses, AG129 mice infected with Heartland virus develop viremia and clinical signs that are consistent with human disease.[7]

Thogotoviridae. Several varieties of thogotovirus are transmitted by ticks. Thogoto virus is an orthomyxovirus that is related to influenza virus and is generally modeled in mice, where it pro-

Table 2. Tick-borne viruses

Disease	Family	Vector	No. infected annually	Mortality rate	Treatment	Vaccine	Models available			Notes	References
							Immuno-competent	Immuno-compromised	Humanized or zooized		
Tick-borne encephalitis virus	Flaviviridae	*Ixodes ricinus* and *I. persulcatus*	5000–10,000	TBEV-Eu and TVEV-Si: 0.5% to 2% TBEV-FE: 40%	None	Available	Mice (Balb/C, C57Bl/6)	None	None	Has been tested in primates but did not cause disease; dogs develop illness	19, 71
Tick-borne encephalitis virus (modeled with Langat virus)	Flaviviridae	NA	NA	0%	None	None	Mice (C57Bl/6), rats (infant)	Mice (Ccr5 $^{-/-}$ or IPS-1$^{-/-}$)	None	Langat virus can infect humans but does not naturally cause disease	35, 42, 47
Powassan virus	Flaviviridae	*Ixodes scapularis*, *Ixodes cookeii*	~70 in USA since 2001)	10% to 15%	None	TBE vaccine may produce limited protection	Mice (Balb/C)	None	None	*Peromyscus* spp. are natural reservoir and can be used to study disease resistance	24, 56
Alkhumra hemorrhagic fever virus and Kyasanur Forest virus	Flaviviridae	Alkhumura: *Ornithodoros savignyi*, *Hyalomma dromedarii* Kyasanur: *Haemaphysalis* spp.	A: 20% since 1995; K: 400–500	A: 30% K: 20%	None	None	Mice (Balb/C)	None	None	Closely related viruses (~90%), with similar modeling	57
Louping ill virus	Flaviviridae	*Ixodes ricinus*	Unknown	78% in *Lagopus lagopus*; variable in sheep	None	Available for sheep	Mice (Balb/C), lambs	None	None	Does not naturally infect humans; mouse model produces less variation than lamb model	60
Crimean–Congo hemorrhagic fever virus	Bunyaviridae	*Hyalomma* spp.	Unknown	10% to 40%	None	None	Guinea pigs	Mice (STAT1$^{-/-}$ or IFNα/βR$^{-/-}$)	None	Usually only pathogenic in humans; humanized animals may be valuable	15, 16, 33

Table 2. Continued

Disease	Family	Vector	No. infected annually	Mortality rate	Treatment	Vaccine	Models available			Notes	References
							Immuno-competent	Immuno-compromised	Humanized or zooized		
Heartland virus	Bunyaviridae	*Amblyomma americanum*	Unknown	Unknown	None	None	Rabbits seroconvert without illness	Mice (AG129)	None	Emerging virus; only a few cases studied; no animal model available; only immuno-deficient mice develop disease	6, 22
Severe fever with thrombo-cytopenia syndrome virus	Bunyaviridae	*Haemaphysalis longicornis* and *Rhipicephalis microplus*	Unknown	≤30%	None	None	Mice (C57Bl/6J)	Mice (INFAR$^{-/-}$ or A129)	None	T705 and antivirals show some efficacy in animals	40, 61, 65
Thogotovirus	Thogotoviridae	*Boophilus* and *Rhipicephalus* spp.	Unknown	Unknown	None	None	Mice (infant), hamsters, sheep	None	None	Closely related to Dhori virus; can be used to model highly patho-genic influenza	31, 52
Dhori virus	Thogotoviridae	*Hyalomma* spp.	Unknown	Unknown	None	None	Mice (ICR)	None	None	Bourbon and Batken viruses are likely very similar	38, 43
Bourbon virus	Thogotoviridae	Unknown N American tick	Unknown	Unknown (supposed ~ 90%)	None	None	None established (likely similar to Dhori virus and Thotogo-virus)	None	None	Emerging virus; only a few cases studied; no animal model available	none
African swine fever virus	Asfirviridae	*Ornithodoros* spp.	Unknown	100%	None	None	Swine	None	SCID-beige mice with porcine bone marrow	Infects domestic pigs only (not humans)	30, 41, 64

Table 3. Midge-borne viruses

Disease	Family	Vector	No. infected annually	Mortality rate	Treatment	Vaccine	Animal models			Notes	References
							Immuno-competent	Immuno-compromised	Humanized or zooized		
Akabane virus	Bunyaviridae	*Culicoides* spp.	>500 (cattle)	Unknown	None	Available	Mice (infant), cattle	None	None	Infects ruminants only; usually nonfatal but results in abortion	27, 37
African horse sickness virus	Reoviridae	*Culicoides* spp.	Unknown	90%	None	Available, provides partial protection	Ponies	Mice (INFAR$^{-/-}$)	None	Infects horses only; research ponies have not been used specifically for this disease but can be adapted from studies of equine infectious anemia	9
Bluetongue virus	Reoviridae	*Culicoides* spp.	Unknown	Variable by breed	None	Available	Sheep	Mice (INFAR$^{-/-}$)	None	Infects ruminants only	20, 28, 45

duces a systemic infection, febrile illness, and weight loss similar to the human infection.[31,52] The livestock effect (abortions in sheep) has not been modeled in mice. For equipped laboratories, a sheep model of this phenomenon may be viable.

Dhori virus, a close relative of Thogoto virus, has similarly been modeled in mice. Intranasal infection of Dhori virus produces rapid and fatal infection in ICR mice, with clinical manifestations similar to those seen in humans infected with highly virulent influenza A virus.[38] Intraperitoneal and subcutaneous inoculation of Dhori virus have also been used, with intraperitoneal inoculation producing the most rapid decline.[43] Due to its pathogenesis and close relation to influenza, Dhori virus has been proposed as a model of severe influenza.

African Swine Fever Virus. African swine fever virus varies from other tick-borne viruses in that, as an asfivirus, it is a large DNA virus. It also differs in the fact that it is highly host-specific, affecting only swine and constituting a strictly agricultural threat. African swine fever virus is asymptomatic in wild porcine species but causes hemorrhagic illness in domestic hogs; swine have been used for pathogenesis studies and vaccine development.[30,41] The virus has also been studied in zooized mice. In this case, SCID mice were injected intraperitoneally with porcine bone marrow cells prior to challenge with African swine fever virus. Development of this zooized animal model allows labs to use a species that is lower on the phylogenetic scale and to bypass the need for the extensive facilities required for work on pigs.[64]

Animal Models for Midge-borne Viruses

Midges are biting, hematophagous flies prevalent in North America. Many of the viruses that they transmit do not cause illness in humans but rather are of agricultural significance (Table 3). Akabane virus is a bunyavirus transmitted by *Culicoides* midges that is responsible for causing encephalomyelitis and birth defects in cattle.[37] Cattle have been used experimentally to study the pathogenesis of the virus and for vaccine development. However, cows did not develop fatal illness unless inoculated intracerebrally or intrasubarachnally.[37] Cattle inoculated through other routes develop histologic changes of the brain but show no illness. This clinical pattern may indicate that a live vector is required or that the infection probability is low. In addition, akabane virus has been modeled by using infant mice, where it has been used to study the comparative lethality of viral mutants injected intraperitoneally.[27]

The other main group of midge-borne viruses are members of the orbivirus genus of the *Reoviridae* family. This group includes equine encephalosis virus (not to be confused with equine encephalitis virus), the closely related African horse sickness virus, and bluetongue virus. Equine encephalosis virus and African horse sickness virus cause lethal horse diseases native to Subsaharan Africa. African horse sickness virus has been studied in INFAR$^{-/-}$ mice for vaccine studies, where it produces viremia, illness, and eventual fatality when injected subcutaneously at 10^4 to 10^5 pfu.[9] Ponies have been used for vaccine studies of equine infectious anemia (a retrovirus vectored by horseflies) and likely could be adapted to studying the disease caused by African horse sickness virus in its natural host.[14] The facilities required for such an undertaking would be extensive.

Bluetongue virus affects various ruminants. Sheep have been used to study the pathogenesis of the virus and for vaccine development.[20,45] In both cases, the sheep were injected intradermally. Vaccine studies have also been performed in INFAR$^{-/-}$ mice, in which bluetongue virus produces lethal disease.[28] Comparatively, the mouse infection model had a much shorter course of disease than the sheep model.

Conclusions

In this review, we outlined currently available animal models for various arboviruses, including those transmitted by mosquitoes, ticks, and midges. Arboviruses are responsible for millions of human infections each year; thus, to alleviate the burden and

costs associated with these diseases, it is important that research focuses on arbovirus disease control and treatment strategies. Animal models for these vector-borne viruses are valuable experimental tools that can shed light on the pathophysiology of the infection and will enable the evaluation of future treatments and vaccine candidates. There is no substitute for using animal models if we are to understand in detail the interactions between the virus, vector, and host or the interactions between the host cells and tissues involved in the response to an arbovirus. Yet significant challenges are often associated with animal model development for arboviruses. Many of the arboviruses fail to cause a lethal infection in common laboratory animal species, or the pattern of disease in the animal model does not accurately represent the course of human infection. Despite such challenges, the number and variety of animal models developed for arbovirus research have increased steadily in recent years. With each of the animal models developed comes a better understanding of the disease and how to best implement preventative and therapeutic measures.

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