Alphaviral equine encephalomyelitis (Eastern, Western and Venezuelan)

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Summary

Alphaviral equine encephalomyelitis is a mosquito-borne infection that causes severe neurological disease and fatalities in horses and humans in the Americas. Consequently, the equine alphaviruses (Eastern, Western and Venezuelan) are of considerable concern worldwide and are notifiable to the World Organisation for Animal Health. In addition, these diseases are considered a potent potential biological weapon, emphasising the need to develop an effective vaccine. Alphaviral equine encephalomyelitis is caused by Eastern equine encephalomyelitis virus (EEEV), Western equine encephalomyelitis virus (WEEV) or Venezuelan equine encephalomyelitis virus (VEEV), which are related members of the *Alphavirus* genus in the *Togaviridae* family. Although related, the three viruses are genetically and antigenically distinct. The disease is characterised by fever, anorexia, depression and clinical signs of encephalomyelitis, and may be fatal in up to 90% of cases, for both humans and horses, particularly in the case of EEE. Surviving horses develop lifelong immunity but may have permanent neuropathology. The aim of this paper is to analyse the scientific information available on the evolution of EEE, WEE and VEE, and any potential vaccines.

Keywords

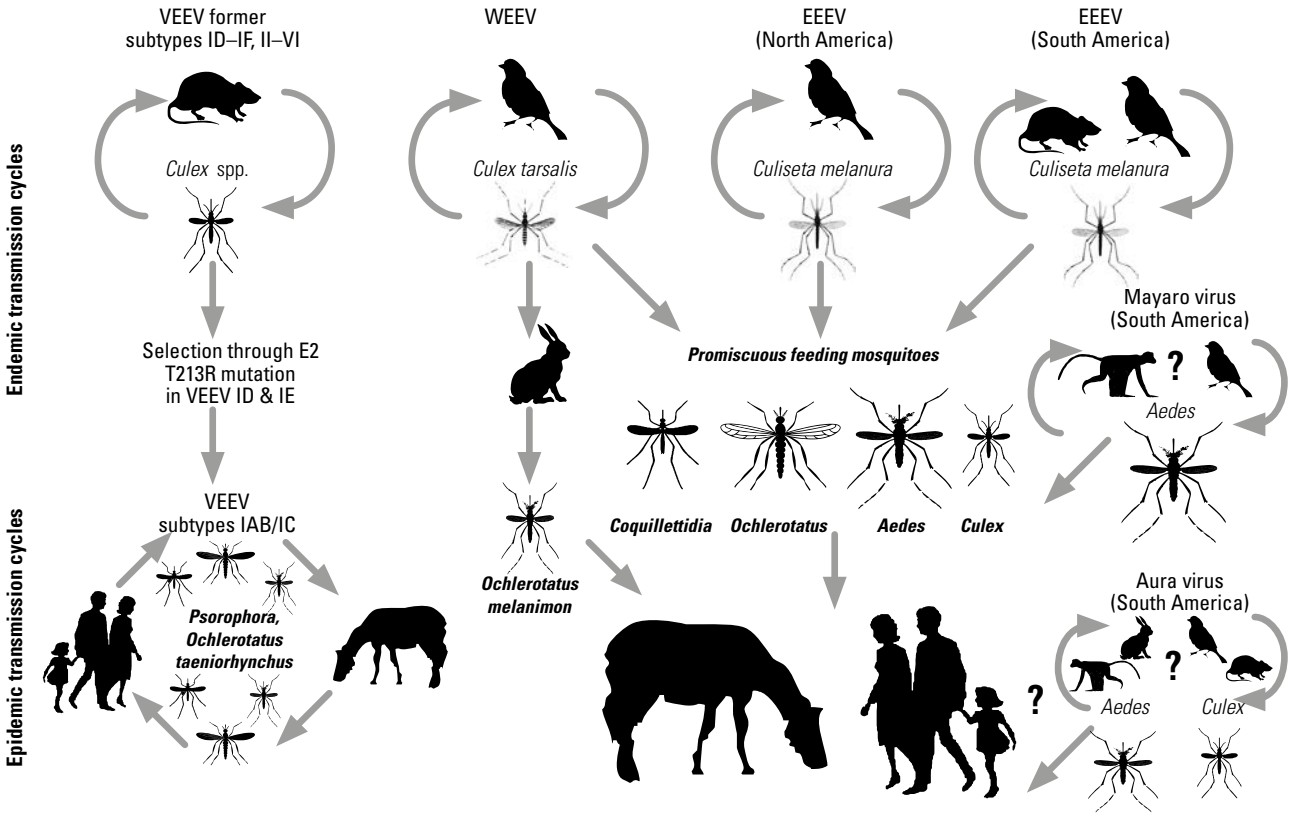
Alphavirus – Eastern equine encephalomyelitis virus – Encephalitis – Equine – Equine encephalomyelitis virus – Horse – Overview – Vector-borne – Venezuelan equine encephalomyelitis virus – Western equine encephalomyelitis virus – Zoonosis.

Alphavirus epidemiological cycles

The genus *Alphavirus* currently includes 29 species grouped into ten complexes. Alphaviruses are maintained in endemic transmission cycles and occasionally spill over into humans and domesticated animals to cause disease. Human infections with Old World alphaviruses such as Ross River, chikungunya and Sindbis viruses are typically characterised by fever, rash and polyarthritis, whereas infections with the New World alphaviruses, such as Venezuelan equine encephalomyelitis virus (VEEV), Eastern equine encephalomyelitis virus (EEEV), and Western equine encephalomyelitis virus (WEEV), can cause fatal encephalomyelitis (1, 2). The epidemiological cycles of the alphaviruses EEEV and WEEV are maintained in nature within a sylvatic or enzootic transmission cycle between ornithophilic mosquitoes and birds (passerine and others), which act as a natural reservoir and as amplifying viral hosts (Fig. 1).

According to our current knowledge, more than 20 mosquito species are implicated in viral transmission, principally *Culiseta melanura*, the vector for EEEV, and *Culex tarsalis*, the vector for WEEV. When the endemic cycle is disrupted, EEEV and WEEV are transmitted to equines and humans via mosquitoes, causing an epidemic outbreak. Horses and humans act as dead-end hosts, and do not develop a high-titre viraemia (3, 4, 5, 6, 7, 8, 9). However, for VEEV, horses and humans act as amplifying hosts, and develop a high-titre viraemia which is capable of transmitting the disease via mosquitoes to other horses or humans (3, 4, 8, 9, 10, 11, 12, 13).

In developed countries, research on the epidemiology of alphaviruses that affect humans has been limited to EEEV, WEEV and VEEV. Cross-immunity between these



EEEV: Eastern equine encephalomyelitis virus
VEEV: Venezuelan equine encephalomyelitis virus
WEEV: Western equine encephalomyelitis virus

Fig. 1
Schematic drawing of the endemic and epidemic transmission cycles of Eastern, Western and Venezuelan equine encephalomyelitis viruses
Other American alphaviruses are included

three viruses has been described (14). Nevertheless, it is possible that other, less-studied alphaviruses that affect the neotropical regions of the Americas, such as Aura alphavirus, which is related to WEEV and EEEV (15), and Mayaro alphavirus, which frequently affects humans in Latin America, could influence the epidemiology of EEEV and WEEV. However, as yet, there are no studies on this subject. Some *in vitro* studies have suggested homologous (various strains of Sindbis) and heterologous (Aura, Semliki Forest and Ross River) interference between alphaviruses. In contrast, an unrelated flavivirus (yellow fever virus) replicated equally well in uninfected and persistently infected cells of each line (16). Since the 1970s, in Latin America, information on cases of WEEV and EEEV infection in humans has been scarce and sporadic. Conversely, VEEV has been reported in humans and was recently isolated from encephalitic horses in Mexico, and may thus eventually be considered a new epizootic variant (17, 18) (Fig. 2).

Diversity

As a result of their antigenic and/or genetic similarities, different variants and subtypes of EEEV and WEEV can be recognised. EEEV is classified into two variants: North American (NA) and South American (SA). NA-EEEV has proved to be more virulent for horses and humans than SA-EEEV (4, 5, 9, 14). Virulence and genotypic differences have been identified among the WEEV complex (19, 20, 21). The VEEV complex is divided into six subtypes (I–VI). Subtype I has different variants (IAB, IC, ID, IE and IF). Subtypes IAB and IC are considered epizootic, causing disease in humans and horses, while D, IE, IF, II, III, IV, V and VI are enzootic and not virulent for horses, but may cause disease in humans (10, 13, 22). Cross-immunity between subtypes has also been demonstrated (5, 9, 23, 24, 25).

The multiplication cycle

Alphavirus virions have a lipid envelope, which contains glycoprotein spikes composed of E1 and E2 viral proteins in a heterodimeric conformation containing two important glycosylation sites. The virion consists of an icosahedral nucleocapsid – formed by repeated subunits of the C protein – which encapsidates the viral genome, without any matrix intermediate (1, 4, 7, 8, 26). The viral genome

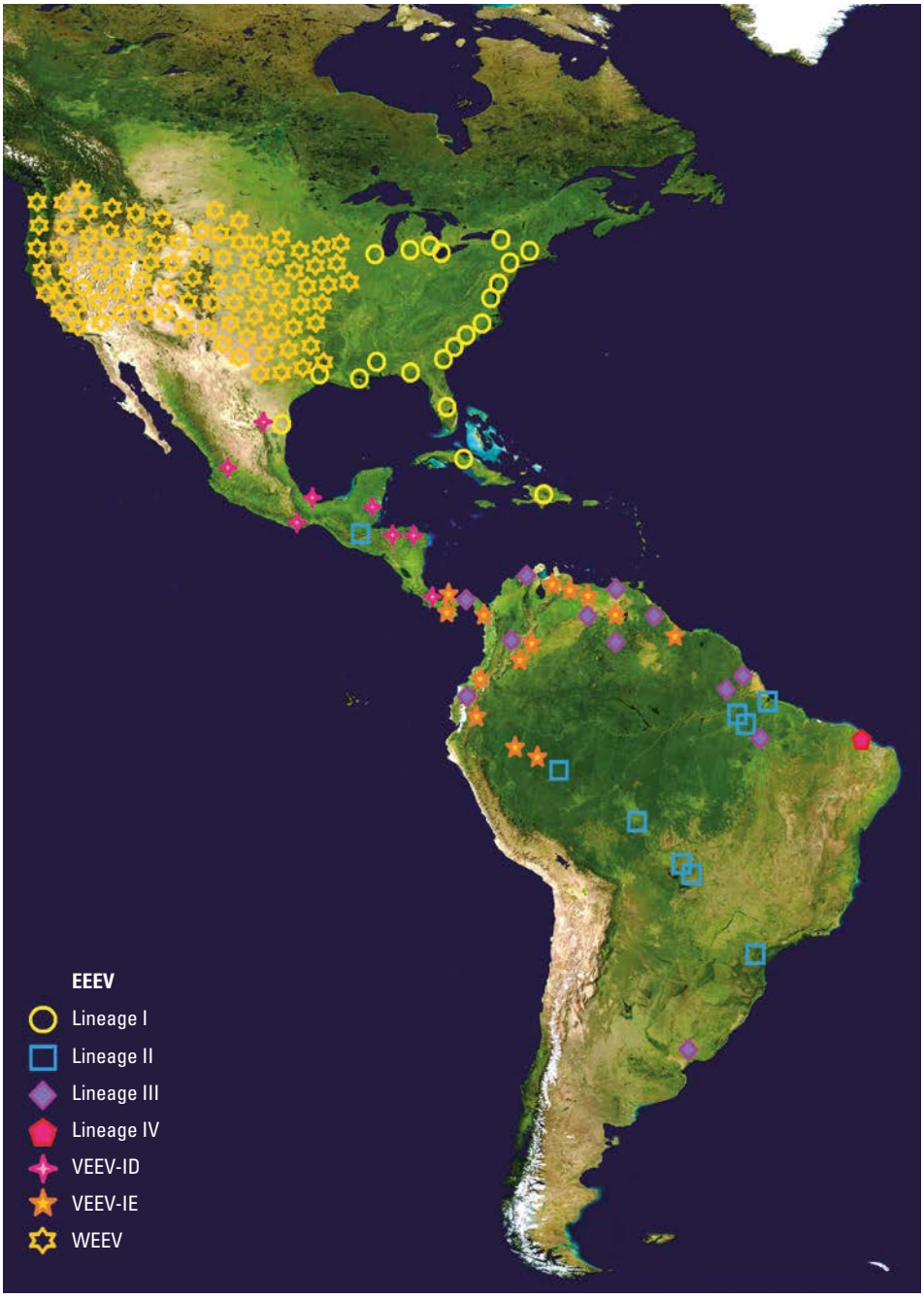


Fig. 2
Distribution of the main alphaviruses that cause equine encephalomyelitis: Western equine encephalomyelitis virus (WEEV); Eastern equine encephalomyelitis virus (EEEV), showing its four lineages; and Venezuelan equine encephalomyelitis virus (VEEV), showing both variants

is a single-stranded, positive-sense RNA which includes two polyprotein gene clusters. The 5´ and 3´ ends encode four non-structural proteins (NSP1–4) and viral structural proteins, respectively. The heterodimer formed by glycoproteins E1 and E2 is strongly immunogenic, inducing the production of neutralising antibodies associated with protection (4, 7, 8, 9, 12, 27, 28, 29, 30, 31). After viral attachment, mediated by E2, and pore formation and viral envelope-endosome membrane fusion mediated by E1, the nucleocapsid is released into the cytoplasm. Once the genomic RNA is released, replication and protein synthesis take place. Structural proteins are synthesised from a subgenomic 26S positive RNA strand, and are translated as a single polyprotein (Capsid-E3-E2-6K-E1), which is post-translationally cleaved into capsid protein (C) and PE2-6K-E1, which undergoes further cleavage in the glycoproteins E1 and E2. The nucleocapsids are assembled and transferred to the plasma membrane containing the

viral glycoproteins E1 and E2, from which they emerge and acquire the lipid bilayer derived from the host-cell plasma membrane (7).

Western equine encephalomyelitis virus

Western equine encephalomyelitis virus was first isolated in 1930 in California, from the brain of an encephalitic horse (32). The virus is maintained in an enzootic cycle between its natural vertebrate hosts, passerine birds, and its most common mosquito vector, *C. tarsalis*, a species associated with irrigated agriculture and stream drainage in the western United States (USA). Transmission to horses and humans is mediated by so-called 'bridging mosquito' vector species, including *Ochlerotatus melanimon* in California, *Aedes dorsalis* in Utah and New Mexico and *Ae. campestris* in New Mexico (Fig. 1).

In moderate climatic areas, WEEV may overwinter in (so far) unidentified hosts or may be reintroduced annually by migratory birds.

Interestingly, WEEV has not been found in Central America, except in the state of Veracruz in Mexico. Genetic analyses of WEEV isolates from South America (Brazil and northern Argentina) suggest that WEEV has a monophyletic lineage with a nucleotide identity of more than 90% in the E2/6K/E1 coding region, when compared to isolates from California, Texas and as far north as Montana. Comprehensive phylogenetic analyses indicate that WEEV viruses are recombinants of EEEV-like (two-thirds of the genome) and Sindbis virus-like (one-third of the genome) parental viruses (33, 34).

Disease in animals and humans

In recent years in North America, human WEEV infection has decreased dramatically; the last documented human case occurred in 1994. Furthermore, the virus has not been detected in mosquito pools since 2008 (35). An isolated, fatal, human case of WEEV was reported in Uruguay in 2011 (36). WEEV infections tend to be asymptomatic or cause mild disease after a short incubation period of two to seven days, with non-specific symptoms, e.g. the sudden onset of fever, headache, nausea, vomiting, anorexia and malaise. In some cases, additional symptoms of altered mental status, weakness and signs of meningeal irritation occur. In a minority of infected individuals, encephalitis or encephalomyelitis occurs and may lead to neck stiffness, confusion, tonic–clonic seizures, somnolence, coma and death. The overall case-fatality rate in humans is estimated to be 3–7%. However, the ratio of inapparent to apparent infections changes with age: 1:1 in children less than one year old; 58:1 for children between the ages of one and four; and >1,000:1 in children aged more than 14 years.

Between 15% and 30% of the survivors of encephalomyelitis are estimated to experience severe neurological sequelae, especially younger children (<1 year old). Encephalomyelitis in humans due to WEEV is characterised by vasculitis and focal haemorrhages in the basal ganglia and the nucleus of the thalamus. Small haemorrhages that are sometimes observed in the white and grey matter may be mistaken for resolved infarcts in elderly patients (37).

Eastern equine encephalomyelitis virus

In 1933, EEEV was first isolated from infected horses in Virginia and New Jersey (38, 39). The primary EEEV transmission cycle occurs between birds and mosquitoes (*C. melanura*). However, the principal arthropod vectors for the transmission of EEEV to humans or horses are *Aedes* spp., *Coquillettidia* spp. and *Culex* spp., which, unlike *C. melanura* (Fig. 1), tend to feed on both birds and mammals (1, 3, 13). Virus transmission most commonly occurs in and around freshwater hardwood swamps in the Atlantic and Gulf Coast states of the USA and in the Great Lakes region. Most cases of EEE have been reported from Florida, Georgia, Massachusetts and New Jersey. Although only a few cases of human infection with EEEV are reported annually in North America – in 2013, the Centers for Disease Control and Prevention (CDC) reported just eight cases for the entire USA (40) – the high mortality rate and serious neurological sequelae in patients infected with EEEV make this virus an important human pathogen (41). EEEV is widely distributed in most tropical forest areas, in regions where horses are predominantly affected, while human cases are rarely detected, even during equine epizootics. However, in 2013, Carrera *et al.* (42) reported an outbreak of EEE that took place in Panama in 2010, in which 19 patients were hospitalised for encephalomyelitis. Seven of these were confirmed as having EEE, three had VEE and one had a mixed infection (WEEV/EEEV). These authors concluded that human cases of EEE in Latin America might be the result of ecological changes that have increased human contact with enzootic transmission cycles, genetic changes in viral strains of EEEV which have led to increased virulence or an altered host range (43). EEEV can cause severe disease in horses, some bird species and in dogs; however, horses are not considered to serve as amplifying hosts during epidemics. Nevertheless, horses do tend to be the first to develop overt disease in a natural focus and thus often serve as indicators of the beginnings of an epidemic.

During the last ten years, cases caused by EEEV have been notified, and several outbreaks were detected in the north-eastern USA. It was reported that the northern expansion occurred in regions where the virus was unknown or had rarely been identified before (41).

Disease in animals and humans

According to the CDC, 220 confirmed human cases of EEEV occurred in the USA from 1964 to 2004. Although generally more prevalent in the south-eastern USA, horse deaths have recently been reported from New Hampshire, Maine and Canada. This virus is probably the most virulent of the encephalitic alphaviruses, with an estimated case-fatality rate of between 50% and 70% in humans. After an incubation period of four to ten days, symptoms begin with the sudden onset of fever, general muscle pains and a headache of increasing severity. In human cases of encephalomyelitis, fever, headache, vomiting, respiratory symptoms, leukocytosis, haematuria, seizures and coma may occur. Clinical studies of serologically and virologically confirmed human EEEV infections have shown changes in the basal ganglia and thalami, suggesting brain oedema, ischaemia and hypoperfusion in the early stages of disease. Brain oedema with necrosis, facial or generalised oedema, vascular congestion and haemorrhages in the brain and visceral organs are seen during gross pathological examination of fatal human cases; histopathological examination reveals vasculitis, haemorrhage and encephalomyelitis (43). Experimental models that have been used to study the pathogenesis of EEEV include: mice, hamsters, guinea pigs and rhesus monkeys; the histopathological studies have used equine and porcine cases. The hamster model was recently described for its advantage of reproducing the vascular component that is lacking in the murine model but is present in the human disease. Neuroinvasion and the development of encephalomyelitis are rapid in both the murine and hamster models, with infection of the periventricular and perivascular neuronal cells in the basal ganglia and hippocampus. In contrast to VEEV, EEEV appears to rapidly invade the brains of infected animals via the blood, and the first antigen-positive neuronal cells are located in the basal ganglia and brain stem in the hamster model. The inflammatory response in the brain is prominent in cases where animals have survived for at least five days, and is produced by macrophages, lymphocytes and neutrophils (37).

Vaccines

The control and prevention of equine alphavirus encephalomyelitis is mainly based on vector control, the reduction of vector exposure, and vaccination. The vaccines for horses currently available are inactivated (Table I) and there are no licensed vaccines for general human use (9, 10, 44). In North America, some efforts have been made to obtain effective vaccines and secure reagents for diagnosis, using recombinant viruses between WEEV, EEEV and Sindbis virus. Chimeric viruses have been created as potential vaccines, some of which are not able to multiply in mosquitoes efficiently (45, 46), but long-term experiments have not yet been conducted. At present, vaccines for human use are limited to the military in the USA and to laboratory workers (47, 48, 49). These vaccines produce an acceptable antibody response that provides protection (29, 30); however, the disadvantage is that the manufacturing process requires the growth and manipulation of high-titre viral preparations, with a median tissue culture infective dose ($TCID_{50}$) greater than 10^6, which must be performed in Biosafety Level 3 laboratory containment (BSL–3) (11, 31). Thus, the production of an effective second-generation vaccine that does not require the handling of infectious viral particles would greatly benefit both the horse industry and human health.

Several new vaccines are being developed, including recombinant and DNA vaccines. WEEV recombinant E1 protein produced in *Escherichia coli* is strongly immunogenic but confers only partial protection in mice after challenge with the homologous strain and no protection at all after challenge with a heterologous WEEV strain (30). Studies with *E. coli* recombinant E2 (30) showed a similar result, with a slightly higher survival rate after challenge (29, 30). A baculovirus expression vector system has also been explored (25). The studies with E1 and E2 glycoproteins indicate that they must be expressed simultaneously in order to maintain the native conformation and immunogenicity, with better results in terms of immune response and protection (50).

A recombinant, replication-defective human adenovirus type 5 (HAd5) vector, encoding E3-E2-6K-E1 of WEEV, was capable of inducing a protective immune response (51), even when no neutralising antibodies were detected. Mice were completely protected, probably due to the presence of non-neutralising antibodies, cell-mediated immunity and the production of type I interferons (52, 53). The role of non-neutralising antibodies in the prevention of alphaviral encephalomyelitis has previously been described (53, 54).

In regard to using modified live vaccines against alphaviruses, a vaccine against VEEV has been developed for use in horses and humans (VEETC-83), derived from the Trinidad donkey strain (subtype IAB TrD), with two effective attenuating mutations (5, 8, 44). TC-83 vaccine induces protective and durable immunity in horses, but may also cause adverse effects, and nearly 40% of vaccinated humans developed signs of the disease. This vaccine is no longer licensed in the USA because of its residual neurovirulence and its potential to revert into a virulent strain. Nevertheless, it is

Table I
Commercial vaccines against alphaviral equine encephalomyelitis available for equines

Name*	Uses	Administration**
Equiloid Innovator® Encephalomyelitis Vaccine-Tetanus Toxoid	For the vaccination of healthy horses as an aid in the prevention of equine encephalomyelitis due to Eastern and Western viruses, and tetanus	Inject one 1 ml dose intramuscularly using aseptic technique. Administer a second 1 ml dose 3 to 4 weeks after the first dose
FLUVAC INNOVATOR® 4 Encephalomyelitis-Influenza Vaccine-Tetanus Toxoid	For vaccination of healthy horses as an aid in the prevention of equine encephalomyelitis due to Eastern and Western viruses, equine influenza due to type A2 viruses, and tetanus	Inject one 1 ml dose intramuscularly using aseptic technique. Administer a second 1 ml dose 3 to 4 weeks after the first dose
FLUVAC INNOVATOR® 5 Encephalomyelitis-Rhinopneumonitis-Influenza Vaccine-Tetanus Toxoid	For vaccination of healthy horses as an aid in the prevention of equine encephalomyelitis due to Eastern and Western viruses, equine rhinopneumonitis due to type 1 and 4 herpesviruses, equine influenza due to type A2 viruses, and tetanus	Inject one 1 ml dose intramuscularly using aseptic technique. Administer a second 1 ml dose 3 to 4 weeks after the first dose
FLUVAC INNOVATOR® 6 Encephalomyelitis-Rhinopneumonitis-Influenza Vaccine-Tetanus Toxoid	For vaccination of healthy horses as an aid in the prevention of equine encephalomyelitis due to Eastern, Western and Venezuelan viruses, equine rhinopneumonitis due to type 1 and 4 herpesviruses, equine influenza due to type A2 viruses, and tetanus	Inject one 1 ml dose intramuscularly using aseptic technique. Administer a second 1 ml dose 3 to 4 weeks after the first dose
FLUVAC INNOVATOR® Triple-E FT® Encephalomyelitis-Influenza Vaccine-Tetanus Toxoid	For vaccination of healthy horses 10 months of age or older as an aid in the prevention of equine encephalomyelitis due to Eastern, Western and Venezuelan viruses, equine influenza due to type A2 viruses, and tetanus	Inject one 1 ml dose intramuscularly using aseptic technique. Administer a second 1 ml dose 3 to 4 weeks after the first dose
TRIPLE-E T INNOVATOR® Encephalomyelitis Vaccine-Tetanus Toxoid	For intramuscular vaccination of healthy horses as an aid in the prevention of equine encephalomyelitis due to Eastern, Western and Venezuelan viruses, and tetanus	Inject one 1 ml dose intramuscularly using aseptic technique. Administer a second 1 ml dose 3 to 4 weeks after the first dose
WEST NILE-INNOVATOR® + EW Encephalomyelitis-West Nile Virus Vaccine	For vaccination of healthy horses as an aid in the prevention of viraemia caused by West Nile virus, and as an aid in the prevention of equine encephalomyelitis due to Eastern and Western viruses	Inject one 1 ml dose intramuscularly using aseptic technique. Administer a second 1 ml dose 3 to 4 weeks after the first dose
WEST NILE-INNOVATOR® + EWT Encephalomyelitis-West Nile Virus Vaccine-Tetanus Toxoid	For vaccination of healthy horses as an aid in the prevention of viraemia caused by West Nile virus, and as an aid in the prevention of equine encephalomyelitis due to Eastern and Western viruses, and tetanus	Inject one 1 ml dose intramuscularly using aseptic technique. Administer a second 1 ml dose 3 to 4 weeks after the first dose
WEST NILE-INNOVATOR® + VEWT Encephalomyelitis-West Nile Virus Vaccine-Tetanus Toxoid	For vaccination of healthy horses as an aid in the prevention of viraemia caused by West Nile virus, and as an aid in the prevention of equine encephalomyelitis due to Eastern, Western and Venezuelan viruses, and tetanus	Inject one 1 ml dose intramuscularly using aseptic technique. Administer a second 1 ml dose 3 to 4 weeks after the first dose

* Early revaccination may be advisable when horses are faced with an outbreak or with other conditions which might make heavy exposure likely
** A 1 ml booster dose should be given annually

still in use in Mexico (5, 22, 55, 56). The influence that this TC-83 vaccine could have upon the ecology of EEEV and WEEV must be studied further.

To avoid reversion, one alternative could be the use of an encephalomyocarditis virus (EMCV) internal ribosome entry site (IRES) that could support the efficient translation of viral proteins in mammalian but not in mosquito cells. This would avoid viral multiplication in the natural vector, since the EMCV IRES would not establish a productive infection in mosquitoes, thus preventing the transmission of such strains of these vector vaccines (47, 48, 49). In one study, an EMCV IRES located in the 5′ end of the EEEV structural open reading frame drove the translation of all structural proteins; moreover, 16 attenuating synonymous point mutations inactivated the subgenomic promoter of

the NA-EEEV. All vaccinated mice developed neutralising antibodies against wild-type EEEV and were protected after homologous viral challenge (47).

High-level expression reporter proteins derived from improved alphavirus expression vectors have been used for tracking the multiplication of alphaviruses from the Old and New World (57). This approach can be very helpful to elucidate interference among different alphaviruses.

Discussion

Several strategies are in development, representing valuable breakthroughs for therapies against the encephalomyelitis caused by VEEV, WEEV and EEEV, although, to date, there are no vaccines to limit infection and/or fatal encephalomyelitis. However, different approaches are being considered to develop such vaccines (22, 44, 48, 51, 58, 59). Another challenge is the development of antiviral drugs. A better understanding of the pathogenesis of VEE, WEE and EEE – and, in particular, those features of the host immune response and tissue-specific responses in the central nervous system that may actually contribute to a fatal outcome after the development of encephalomyelitis – suggests the need to develop antiviral strategies. Some examples are: the delivery of cytokines or cytokine-blocking agents (51, 60), treatment with agents that block specific stages of the virus life cycle (61), and antibody-based therapeutics. Numerous studies of human infection demonstrate that VEEV elicits an antibody response, although it is not clear whether the antibody response alone would protect individuals against the development of encephalomyelitis and consequent death. Pathogenesis studies using the alphavirus model of the Sindbis virus (1), as well as treatment and related studies with VEEV-specific antibody, suggest that VEEV-specific antibody therapy may be useful (62). Recent studies in mice indicate that high-titre VEEV-specific antibody is partially protective against lethal intranasal VEEV infection (S. Paessler, unpublished data). However, the limited ability of these mice to survive when treated at a lower VEEV-specific antibody dose, alongside the ability of some mice with a deficiency of mature B cells to survive VEEV infection (62), indicates that additional studies are needed to strengthen the rationale for this approach.

Conclusion

The best-studied alphaviruses, such as EEEV, WEEV and VEEV, are those that affect developed countries, and there is evidence of close relationships between these viruses.

Nevertheless, the great biodiversity in tropical environments has given rise to many other less-studied viruses, such as Aura virus (which is also very close to EEEV and WEEV), and Mayaro virus, which frequently affects humans and probably other species. However, there is little information about the impact of these similar viruses on the clinical manifestation and ecology of EEEV and WEEV infections. This underlines the importance of further research on all these viruses, to confirm, for example, that the South American variants of EEEV are less virulent than the North American ones. There is a possibility that clinical manifestations of EEEV could be less harmful in Latin America because of the prevalence of antibodies against other related alphaviruses that could be conferring cross-protection.

TC-83 vaccines against VEEV have been used in Mexico since the 1970s and are still being produced by Productora Nacional de Biológicos Veterinarios (PRONABIVE). However, we have not yet clarified the influence of this vaccine on the clinical manifestations of EEEV and WEEV.

It is possible that the chimeric vaccines that have been proposed could affect some ecological factors of the epidemiology of EEEV and WEEV, and so viral replication in the mosquito must be carefully studied.

Another feature that should be considered is whether other recently introduced viruses such as chikungunya might be altering the transmission dynamics of the earlier viruses, since they can share the same vectors.

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Les encéphalomyélites équines (de l'Est, de l'Ouest et vénézuélienne) dues à des alphavirus

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Résumé
Les encéphalomyélites équines dues à des alphavirus sont des infections transmises par les moustiques qui induisent une grave maladie neurologique ainsi que des cas de mortalité chez le cheval et l'être humain dans les Amériques. Les alphavirus équins (de l'Est, de l'Ouest et vénézuélien) font donc l'objet d'une très grande attention au niveau mondial et leur détection doit être notifiée à l'Organisation mondiale de la santé animale. En outre, le risque que ces maladies soient utilisées en tant qu'armes biologiques est important, ce qui accentue l'impératif de développer un vaccin efficace. Les agents responsables de ces maladies sont respectivement les virus de l'encéphalomyélite équine de l'Est (EEEV), de l'Ouest (WEEV) et vénézuélienne (VEEV), trois membres apparentés du genre *Alphavirus* appartenant à la famille des *Togaviridae*, mais néanmoins distincts aux plans génétique et antigénique. La maladie se manifeste par une fièvre, une anorexie, un abattement et les signes cliniques de l'encéphalomyélite ; l'issue est fatale dans 90 % des cas aussi bien chez l'homme que chez le cheval, en particulier dans les cas d'encéphalomyélite équine de l'Est. Les chevaux qui survivent à l'infection développent une immunité pour le restant de leur vie mais peuvent toutefois présenter des troubles neurologiques permanents. Les auteurs analysent l'information scientifique disponible sur l'évolution de ces maladies à alphavirus ainsi que sur les perspectives de développement de vaccins.

Mots-clés
Alphavirus – Cheval – Encéphalite – Équidé – Maladie à transmission vectorielle – Synthèse – Virus de l'encéphalomyélite équine – Virus de l'encéphalomyélite équine de l'Est – Virus de l'encéphalomyélite équine de l'Ouest – Virus de l'encéphalomyélite équine vénézuélienne – Zoonose.

Encefalomielitis equina alfavírica (del Este, del Oeste y venezolana)

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Resumen
La encefalomielitis equina por alfavirus es una infección transmitida por mosquitos presente en el continente americano que causa una grave enfermedad neurológica, a veces mortal, en el caballo y el ser humano. De ahí que los alfavirus equinos (del Este, del Oeste y venezolano) susciten considerable preocupación en todo el mundo y sean de declaración obligatoria a la Organización Mundial de Sanidad Animal. Además, se considera que estas enfermedades pueden constituir una potente arma biológica, lo que hace aún más necesario dar con una vacuna eficaz. Los agentes etiológicos de la encefalomielitis equina alfavírica son el virus de la encefalomielitis equina del Este (VEEE), el virus de la encefalomielitis equina del Oeste (VEEO) y el virus de la encefalomielitis equina

venezolana (VEEV), que son miembros emparentados del género *Alphavirus*, familia *Togaviridae*, pero difieren en sus propiedades genéticas y antigénicas. La enfermedad, que se caracteriza por la presencia de fiebre, anorexia, depresión y signos clínicos de encefalomielitis, puede ser mortal en hasta el 90% de los casos, tanto en humanos como en caballos, sobre todo en el caso de la EEE. Los caballos que sobreviven adquieren inmunidad vitalicia, pero a veces subsiste una neuropatología crónica. Los autores analizan la información científica existente sobre la evolución de la EEE, la EEO y la EEV y sobre posibles vacunas.

Palabras clave
Alphavirus – Caballo – Encefalitis – Equino – Exposición general – Transmisión vectorial – Virus de la encefalomielitis equina – Virus de la encefalomielitis equina del Este – Virus de la encefalomielitis equina del Oeste – Virus de la encefalomielitis equina venezolana – Zoonosis.

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