Equine Herpes Virus-1. A clinician’s perspective.

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Equine Herpes Virus-1. A clinician’s perspective

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ABSTRACT: Equid herpesvirus type 1 (EHV-1) is a common pathogen of horses with worldwide distribution. In light of last years’ outbreaks reported across Europe and United States of America, the contagious nature of this disease is highlighted and re-evaluation of diagnostic procedures, treatment modalities and biosecurity protocols is imperative. This review provides an overview of the epidemiology, current treatment protocols and prognosis for EHV-1-associated syndromes, with an emphasis on the neuropathogenic strain of EHV-1.

Keywords: Equine; herpesvirus; outbreak; clinician

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INTRODUCTION

Equine herpesvirus-1 is a highly prevalent equine pathogen with a worldwide distribution, inducing diverse clinical signs from mild respiratory distress to severe myeloencephalopathy, abortion and neonatal death (Pusterla & Hussey, 2014). Despite the potential severity of outbreaks and the relevant financial impact on the equine industry, there are currently no vaccines to effectively protect against neurological disease (Laval et al., 2021). This is recently highlighted by the evolution of a very aggressive EHV strain of the neurological form, originating in competition horses in Spain (Vautmans 2021, FEI 2021). The rapid spread of this neurological form has been blamed for several fatalities connected to last year’s related outbreaks in more than 8 European countries. USA has also announced several cases of EHV-1 neurological form in over 12 States (EDCC, 2021). The aim of this review is to raise awareness and early detection of several presentations of EHV-1 infection among equine clinicians.

PATHOGENESIS

Based on their biological properties herpesviruses are divided into three subfamilies, alpha, beta and gamma (α, β, and γ) (Payne, 2017). To date, nine different species of EHV have been reported, while 5 of them have been linked to associated equine disease (Davison et al., 2009). Equine herpes virus 1 is a double-stranded DNA virus, standing out as one of the most ancestral alpha-herpesvirus in the phylogenetic reconstruction (Karlin et al., 1994). Currently, it is estimated that prevalence of latent EHV-1 infection worldwide is over 60% (Pusterla et al., 2014).

EHV-1 primarily replicates in a plaquewise manner in the epithelial cells lining the upper respiratory tract (Gryspeerdt et al., 2010). Data from in vivo experiments suggest that EHV-1-induced plaques are visible in the epithelium of the nasal mucosa 2-7 days post-inoculation (Gryspeerdt et al., 2010). In addition, in ex vivo experiments, single infected EHV-1-induced plaques are observed in the epithelium of equine nasal and nasopharyngeal explants starting from 24 hours post-inoculation (Vandekerckhove et al., 2010; Laval et al., 2021). Hence, primary inoculation of the upper respiratory tract tissues causes erosion of the epithelium, nasal shedding and local inflammation with mild clinical symptoms in adult horses; younger horses usually develop more severe clinical manifestations (Laval et al., 2021). Previous studies indicate that the virus hijacks individual mononuclear leukocytes from the upper respiratory tract to cross the basement membrane into the connective tissues (Vandekerckhove et al., 2010). Ultimately, EHV-1 strains develop a highly cell-associated viraemia and have a predilection for vascular endothelium (Bryant et al., 2018); hence, the virus replicates at the endothelial cells of the target organs, such as the nervous system and/or pregnant uterus (Allen et al., 2004; Van Cleemput et al., 2017). Although equine herpesvirus myeloencephalopathy (EHM) is considered a sporadic and relatively uncommon manifestation of EHV-1, recent outbreaks outlining potential more aggressive neuropathogenic strains, raise awareness. Equine herpesvirus type 4, closely related to EHV-1, can also cause mild respiratory symptoms, but a cell-associated viremia in leukocytes is rare (Oladunni et al., 2019). Consequently, a key determinant of EHV’s pathogenicity is the use of immune cells as “Trojan horses” to disseminate inside the host. The establishment of a reactive, latent infection in their host is the hallmark of herpesviruses (Grinde, 2013). Virus transmission to susceptible equids is usually accomplished through direct contact with virus-laden respiratory secretions or indirectly with fomites (Allen et al., 2004). These cycles of latency and reactivation promote shedding and transmission to new hosts, allowing the virus to be maintained in herds.

EPIDEMIOLOGY

Equine herpesvirus 1 (EHV-1) was first described by Dimock and Edwards in the early 1930s (Dimock & Edwards, 1933). Subsequent identification of gross pathological changes in the aborted fetuses resulted to the established term ‘equine viral abortions’ to describe the disease (Dimock & Edwards, 1933; Dimock, 1940). Henceforth, the ‘equine abortion virus’ was cultivated in laboratory animals and tissue culture (Westerfield and Dimock, 1946); Randall et al., 1953). The virus was finally recognized by the International Committee on Taxonomy of Viruses in 1988 (Roizman, 1991). Equine herpesvirus type 1, has been isolated from aborted fetuses in equine populations worldwide (Bazańów et al., 2014; McFadden et al., 2016).

The association between virus abortion and the respiratory form of EHV-1 was first assumed by Manninger and Csontos (1941) in Europe. They documented similar symptoms as those observed in “equine viral abortions” along with signs of respiratory infection and mild fever (Manninger and Csontos, 1941). At the same time, Kress (1941) indicated that
The abortion virus has a clear potential pneumotropism due to the prevalence of bronchopneumonia in horses that get in contact with aborted materials.

The first definitive association between EHV-1 and myelenecephalopathy was made in 1966 in Norway when the virus was isolated from the brain and spinal cord of a horse with severe neurologic dysfunction (Saxegaard, 1966; Wilson 1997). The neurological form of EHV-1 infection now is considered to have a worldwide distribution (Laval et al., 2021). Recent emergence of a potential more virulent mutant strain of the virus EHV-1 (Pusterla et al., 2021) has resulted in EHM outbreaks in several countries. The increased neuropathogenic ability of EHV-1 has resulted in higher than previously reported morbidity and mortality rates.

Pathogenic potential among EHV-1 and other equine alphaherpesviruses has been previously reported (Osterrieder et al., 2010; Ma et al., 2013). Since the early 70’s most strains were distinguishable as respiratory (subtype 2) and abortigenic (subtype 1) (Burrows and Goodridge, 1973). On the contrary, pathogenic potential existence amongst EHV-1 family associated with neurological disease is still under investigation (Paillot et al., 2020; Mesquita et al., 2021).

One of the key points of the recent EHV-1 outbreak in the United States is that the investigation started when horses displayed pyrexia with no other apparent clinical signs (Pusterla et al., 2021). The genetic characterization of the EHV-1 strain showed a new mutation, similar to the mutation reported in the recent outbreaks in Europe (Sutton et al., 2020).

Clinical presentation and diagnosis

In general, EHV-1 infections may occur asymptptomatically or be accompanied by respiratory disease of varying severity (Van Maanen, 2002). However, as previously stated, EHV-1 infection can also result in comparatively more serious clinical manifestations such as abortions, neonatal death or neurological disease.

Respiratory disease

Clinically, the respiratory disease caused by EHV-1 can be mild or asymptomatic in older or previously exposed horses (Allen et al., 2004). In contrast, the respiratory disease observed in young immunologically naive horses is often severe, characterized by a biphasic fever, anorexia, lymphadenopathy and ocularnasal initially serous discharge (Gibson et al., 1992). Viral isolates recovered from horses with severe respiratory manifestations typically induced only mild respiratory disease in experimental conditions (Pusterla et al., 2014). That fact along with the longer incubation period observed in natural infections (Slater 2007) suggests potential secondary bacterial infection involvement. Some animals may present with cough, although this is not a consistent clinical feature. An initial biphasic leucopenia is followed by an increase in leukocytes 8 days following EHV-1 infection (Gibson et al., 1992). The clinical signs of upper respiratory disease subside within 14 days and horses usually recover uneventfully (Slater, 2007). Nonetheless, prolonged poor performance has been reported in horses affected by concurrent or secondary infections (Slater, 2007).

Differential diagnosis of EHV-1 and its close relative EHV-4 is hampered by their overlapping disease spectra and their close genetic and antigenic relationship. Clinically, the respiratory disease caused by EHV-1 and EHV-4 is indistinguishable; However, EHV-1 infection results in a systemic viremia that is more likely to progress in severe sequelae, such as abortions and/or neurological disease. Alternatively, EHV-4 infection usually remains restricted to the upper respiratory tract (O’Callaghan et al., 2008). Clinical signs of EHV-1 frequently resemble the ones associated with equine arteritis virus; acutely infected animals may also develop a wide range of clinical signs including pyrexia, respiratory distress and abortion, frequently along with dependent edema, stiffness of gait, periorbital and supraorbital edema and urticaria (Balasuriya et al., 2018). Equine influenza virus is another highly contagious pathogen with similar clinical manifestations. In a susceptible population, presumptive diagnosis may be made based on clinical signs, especially coughing and vaccination history (Gilkerson et al., 2015). Recent studies investigate the potential involvement of other herpesviruses, such as EHV-2 and EHV-5 to be associated with equine respiratory disease (Hartley et al., 2013; Xie et al., 2021). Furthermore, equine rhinitis viruses A and B and equine adenoviruses are also prevalent in the horse population worldwide and can cause clinical disease that is indistinguishable from other respiratory pathogens (Bash et al., 2019). Although the viruses are not well studied, they are known to cause mild to severe respiratory disease affecting both the upper and lower airways. They may also contribute
to, or exacerbate, inflammatory airway disease and recurrent airway obstruction. In recent years, various studies have used metagenomics to identified new viruses (cyclovirus, paroviruses) associated with acute respiratory disease (Altan et al., 2019). Finally, the differential diagnosis, especially when secondary bacterial infections are suspected, also includes other infectious agents such as Streptococcus equi subsp. equi; and Streptococcus equi subsp. zooepidemicus (Boyle et al., 2018).

**Abortion**

Equine herpesvirus-1 is considered one of the common agents responsible for late-term abortions in mares (Smith et al., 2003). Abortion usually occurs in the last trimester of pregnancy without warning and the placenta is expelled together with the fetus (Smith et al., 2003). Most abortions occur as sporadic cases and are presumed to have resulted from re-activation of the latent virus, rather than from de novo infection. Occasionally, “EHV-1 abortion storms” have been described with lateral transmission of the virus between horses (Damiani et al., 2014). Pregnant mares infected with the virus may abort spontaneously without prior signs of primary respiratory disease (Smith et al., 2003).

The important factors deployed by host immune and inflammatory response, and vascular coagulation cascades mediating EHV-1-induced abortion have not been fully elucidated (Allen et al., 2004). It is believed that microthromboses within blood vessels may promote ischemic necrosis of the cotyledons and intercotyledonary stroma, causing the fetus to detach from the placenta and die of anoxia (Allen et al., 2004). Gross lesions in the aborted fetuses from mares include multifocal necrotic areas in the lungs, liver and lymphoid tissues, pulmonary edema, together with edematous and congested placentae (Stasiak et al., 2020). There are no long-term effects following EHV-1 abortion on the reproductive performance of the affected mare (Schulman et al., 2013). Differential diagnosis includes a wide variety of abortigenic agents such as Escherichia coli, Klebsiella pneumoniae, Bartonella spp., Leptospira spp., Salmonella spp., Streptococcus equi subspecies zooepidemicus, Streptococcus dysgalactiae subsp. equisimilis, Chlamydia psittaci, along with many parasitic agents (Marenzoni et al., 2012). Vaccination history, co-existent pathologies in farms and reported “abortions storms” are coefficients to be taken into consideration in every sudden, unexpected abortion with icteric fetus.

**Neonatal disease**

The ability of EHV-1 to establish an early infection in foals constitutes an important epidemiological advantage (Gilkerson et al., 2000). Foals born alive despite infection in utero, they are usually abnormal from birth and may show signs of weakness, jaundice, dyspnea and neurological signs (Slater, 2007). Perinatal infection may result in severely leukopenic foals (Dixon et al., 1978) that typically die within the first few days of life; it is likely for those that survive to develop pneumonia complicated by secondary bacterial infections (Slater, 2007).

**Ocular Disease**

Young foals that come in close contact with equine EHM-infected horses are at high risk of developing ocular disease (McCartan et al., 1995). Respiratory infection with highly pathogenic EHV-1 strains is associated with severe ocular lesions such as chorioretinitis or uveitis (Hussey et al., 2013). It is believed that virus replication in the chorioretinal vasculature results in ischemic necrosis and consequently visual impairment (Hussey et al., 2013). Ocular lesions primarily affect the choroidal vasculature and appear between 4 weeks to 3 months post infection. Lesions can be focal, multifocal and rarely clinically important diffuse lesions (Pusterla et al., 2014). Differentials for chorioretinal infiltrates include other systemic infectious diseases caused by viruses (EHV-2, equine influenza, equine viral arteritis, Para-influenza type 3), bacteria (Leptospira spp., Brucella spp., Streptococcus spp., Rhodococcus equi, Borrelia burgdorferi), parasites (Onchocerca spp., Strongyulus spp., Toxoplasma gondii), or neoplasia (Gilger et al., 2010).

**Neurological disease**

Equine herpesvirus myeloencephalopathy (EHM) can occur as a single sporadic case or as an outbreak, which is likely to represent reactivation of a latent virus and lateral spread sources of infection, respectively (Burgess et al., 2012; Traub-Dargatz et al., 2013). Hence, incubation period is difficult to determine, as the primary infection might have occurred months before the re-activation. Fever seems to be as one of the most consistent clinical signs in several EHM outbreaks (Negussie et al., 2017; Preziuso et al., 2019; Pusterla et al., 2021). Typically, the interval between the first detection of pyrexia and the development of neurological signs ranges from 4 to 9 days (Walter et al., 2013). The clinical signs are highly variable depending on the site of neurologic impact (Allen et al.,...
2004). They range from mild ataxia to severe neurological deficits and conscious proprioceptive deficits and recumbency (Allen 2008; Göhring et al., 2010). More specifically, the caudal spinal cord is typically most severely affected.

Typical cases of EHM often include an initial fever followed by weakness and ataxia, dysuria, fecal retention, tail- and anal-tone deficits, and “dog-sitting” posture. Cranial nerve deficits and primary brain dysfunction can be present. Clinical signs of EHM appear following the onset of viremia, often following a secondary fever spike and in the absence of respiratory disease (Pusterla et al., 2014). Unless there is known trauma or another well-defined cause, any case of acutely progressive myelopathy and encephalomyelopathy or minus cranial nerve deficits should include EHM (Pusterla et al., 2014). The list of differential diagnoses involves west nile virus, other arboviral encephalitides, EHV-4, equine protozoal myeloencephalitis, central nervous system trauma, lead poisoning, tetanus, rabies, botulism polyneuritis equi, and Aujeszky’s disease (Van den Ingh et al., 1990; Long, 2014; Barba et al., 2019; Lecollinet et al., 2020).

Although initial clinical signs include pyrexia in most cases, it is impossible to rule out EHM, and thus, testing for this disease must be included in the work-up. The key diagnostic criteria for EHM should be based on the acute onset of typical neurological signs (usually including ataxia, paresis, and urinary incontinence), a history of pyrexia and sometimes, abortion or respiratory signs or involvement of other horses.

There are many studies investigating the presence of EHV-1 strains with neuropathogenic potential (Allen et al., 2008; Gryspeerdt et al., 2010; Castro and Arbiza, 2017; Negussie et al., 2017; Preziuso et al., 2019; Pusterla et al., 2021). Although, some EHV-1 isolates appear to be more likely to induce EHM than others, all EHV-1 should be considered to be potentially neuropathogenic (Pronost et al., 2010).

In general, prognosis for resolution of EHM depends upon the severity of the neurological impairment and the level of supportive care available. In general, the outcome is fairly favorable for non-recumbent horses that are provided with the appropriate supportive measures, but poor for the ones that are recumbent (van Maanen et al., 2001).

**Diagnosis**

Traditional tests such as virus isolation, various serological methods and developed PCR assays are all used for diagnosis (McCann et al., 1995). The antigenic similarity between EHV-1 and its close relative EHV-4, along with the lack of availability of a type-specific antibody test tended to impede serological data interpretation till the early 90’s (Crabb & Studdert, 1993).

When suspicious of disease, veterinary clinicians should submit appropriate samples. Nasal swab/naopharyngeal wash and whole-blooduffy-coat samples should be submitted to an approved laboratory for EHV-1 testing in suspected cases, along with the appropriate signalment (Pusterla et al., 2008; Kydd et al. 2012). Definitive serological diagnosis of recent EHV-1 infection requires at least a 4-fold rise in titers between acute and convalescent samples. The testing is complicated by the routine use of EHV-1 vaccination and by extensive cross-reactivity due to the high percentage of sequence identity between EHV-1 and EHV-4 (Telford et al., 1998). Recently, a type-specific ELISA has been developed, although not widely commercially distributed (Hartley et al., 2005).

In the case of abortion this will include the whole foetus/foal carcass and foetal membranes. Modern qPCR can be run in a matter of hours allowing biosecurity measures to be put in place very promptly (Hussey et al., 2006). Some of the assays have the additional capability of distinguishing between the mutant neuropathogenic and wild type (Smith et al., 2012).

Virological examination of the placenta with virus-specific nested PCR methods could be a useful option in equine abortion investigations (Gerst et al., 2003).

Since the positive predictive value of PCR-based tests for EHV-1 in asymptomatic horses is uncertain at this time, horses outside of quarantine areas or in unexposed stables should not be tested on a random basis; low levels of non-replicating virus may be the source of the viral DNA detected (Hussey et al., 2006). This means that the detection of virus through PCR analysis does not provide a diagnosis in the absence of clinical signs and/or of other corroborating information.

**Biosecurity management measures**

In spite of the vaccination strategies, various management practices or suggestions are essential to prevent EHV-1 infection and outbreak in horses (Kushro
et al., 2020).

- In order to minimize the risk of viral infection onto the farm, it is essential to quarantine any new horse away from the other horses for a minimum of 21 days.
- A closed herd can be a significant management practice. The non-transient animals can be kept in areas away from the horses that are constantly moving.
- Separating the broodmares from the show horses can decrease the possibility of transmission.
- Transportation, personnel and handling equipment needs to be disinfected regularly.
- Sharing feeders or watering tanks and grooming equipment on new horses should be avoided.
- New horses should be vaccinated during the quarantine period.
- Exposure to other animals should be limited.
- The lead ropes, saddle pads, and blankets, belonging to other horse owners, should be avoided.
- The number of visitors should be limited. A logbook for all the visitors needs to be maintained too.
- Infected horses should be kept in their existing stables and segregated from other horses during exercise periods.
- If horses develop clinical symptoms the veterinarian should be notified, and the movement of other horses in that area should be avoided until the infection is confirmed.
- Horses showing clinical symptoms of EHV-1 should be removed immediately and kept in an isolated area.
- Since stress plays a pivotal role horses kept in the infected area should not be subjected to strenuous physical exercise or long-distance transportation.
- EHV-1 positive horses within designated quarantine areas should be retested periodically.

### Treatment

Once biosecurity and quarantine measures have been implemented, there are numerous supportive treatment options for EHV-1 positive horses (Table 1). Upon clinical symptoms of EHM, it is important to consider intensive nursing care. This may include provision of soft bedding to protect the horse from decubitation and head trauma, the use of indwelling urinary catheters and manual evacuation of the rectum and assisting the horse with slings. If the horse is unable to stand the horse should be maintained in sternal recumbency, and rolled to different sides every 2-4 hours. Monitoring and maintaining hydration is vitally important.

#### Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs such as phenylbutazone or flunixin meglumine play an important adjunctive role as antipyretic and prostaglandin blocking agents. Furthermore, they can reduce thrombocyte aggregation during vasculitis at the CNS level pain (Göhring et al., 2017). The use of acetylsalicylic acid (aspirin) in suspect EHM cases

<table>
<thead>
<tr>
<th>Treatment Details</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive treatment as required (IV polyionic fluids, repositioning, tranquilisation, bladder catheterization, slinging as required)</td>
<td>Studdert et al. 2003</td>
</tr>
<tr>
<td>Fluids (20 mL/kg Hartmann’s solution)</td>
<td>Studdert et al. 2003</td>
</tr>
<tr>
<td>Phenylbutazone (4 mg/kg peros, sid), Flunixin meglumine (1.1 mg/kg IV SID)</td>
<td>Henninger et al. 2007</td>
</tr>
<tr>
<td>Dexamethasone (0.2 mg/kg I/V, SID for 3 days, then 0.1 mg/kg I/V, SID for 3 days)</td>
<td>Lunn et al. 2009.</td>
</tr>
<tr>
<td>Acyclovir (20 mg/kg per os, tid for 5 days)</td>
<td>Henninger et al. 2007</td>
</tr>
<tr>
<td>Valacyclovir (30 mg/kg per os q8h for the 1st 48 hours, decreased to 20 mg/kg per os)q12h</td>
<td>Maxwell et al. 2008; Lunn et al. 2009; Garré et al. 2009</td>
</tr>
<tr>
<td>10% DMSO (1 g/kg I/V sid for 3 days)</td>
<td>Henninger et al. 2007; Lunn et al. 2009</td>
</tr>
<tr>
<td>Heparin (25000 IU SC BID for 3 days)</td>
<td>Walter et al. 2013; Stokol et al., 2016</td>
</tr>
<tr>
<td>DMSO (0.25 g/kg in LRs IV SID for 5 days) ±acyclovir (20 mg/kg per os, TID for 5 days) ±dexamethasone (0.3 mg/kg IV SID for 3 days, then 0.1 mg/kg IV SID for 3 days)</td>
<td>Henninger et al. 2007</td>
</tr>
</tbody>
</table>

DMSO=dimethyl sulphoxide; SID=once daily; BID=two times daily; TID=three times daily; I/V=intravenously; SC=subcutaneously
at the time of fever detection (Göhring et al, 2005) has been proposed, although its use remains controversial (Hernandez et al., 2016).

Corticosteroids
Corticosteroids are suggested to be protective against the cellular response to CNS infection, thereby preventing the development of edema, vasculitis and thrombosis (Lunn et al., 2009). In cases of myelencephalopathy, corticosteroids may be appropriate, as they limit the degree of thrombo-ischaemic lesions caused by infection of endothelial cells. Corticosteroids should be prescribed with caution (McCartan et al. 1995) however, the risk of a viral reactivation due to the administration of corticosteroids seems to be low (Edington et al., 1985).

Dimethyl sulfoxide (DMSO)
DMSO is a free radical scavenger and may inhibit thrombocyte aggregation (Henninger et al., 2007). Treatment with DMSO infusion has been described in cases of neurologic disease (Henninger et al., 2007). Due to its potential teratogenic effect, DMSO should not be used in pregnant mares (Autio et al., 2007).

Antibiotics
Due to immunosuppression, antibiotics may be administered in cases of secondary bacterial infection of the upper respiratory tract or when a urinary bladder catheter is placed for a long period of time (Walter et al., 2013).

Mucolytics/sympathomimetics
Mucolytic agents such as dembrexine and sympathomimetic drugs, like clenbuterol, that increase the mucociliary clearance and reduce contamination of the respiratory airways can assist in respiratory cases (Ivens, 2014).

Antioxidants
The positive effects of vitamin E in inflammatory processes can be favorable at any stage of disease. However, the necessary concentration within CNS tissue may be achieved only after several days (Ivens, 2014).

Heparin
Low molecular weight heparin is reported to reduce thrombosis and might have a beneficial effect in EHM clinical manifestations (Walter et al., 2013; Stokol et al., 2016).

L-Lysine
L-Arginine is an important amino-acid necessary for herpes viral replication, whereas L-Lysine inhibits its intestinal absorption of L-Arginine (Griffith et al., 1987). L-Lysine is a component of several food stuff additives and seems to have a stronger therapeutic effect within the very first stages of infection. The most recent reviews in human medicine have concluded that there is no reliable evidence to support the use for herpesvirus management (Mailoo et al., 2017.)

Antiviral drugs
The administration of anti-viral agents seems to be useful in impeding virus replication; however their use still remains a subject of continued investigation (Shiraki, 2018). Second-generation nucleoside analogues, like acyclovir and valacyclovir present questionable bioavailability, although in some cases seemed to reduce the severity of EHM symptoms (Garre et al., 2009; Maxwell et al., 2017). Ganciclovir in vitro seems to be the most potent drug in the class (Carmichael et al, 2013).

Immunostimulants
Immunostimulants such as Parapoxvirus ovis in studies of natural EHV-1 exposure caused a reduction in clinical signs of respiratory disease (Ons et al, 2014). Their use has not been evaluated in the context of EHM outbreaks and it is not licensed for this purpose.

Vaccination
To date, there are commercially available EHV-1 and EHV-1/4 vaccines (Supplementary Table 1) (Slater 2007). The value and limitations of current commercial vaccines are widely recognized, and were extensively reviewed (Kydd et al., 2006; Goehring et al., 2010).

From 2015 to early 2017, numerous European countries faced an EHV vaccine shortage. The two veterinary pharmaceutical companies providing these vaccines in Europe experienced manufacturing issues with vaccine batch production and release. Both companies obtained temporary authorization to import and commercialize substitute EHV-1 vaccines (Paillot et al., 2017).

Therefore, vaccination can be effectively used as an adjunctive measure to control EHV-1 infections by minimizing the shedding of the virus (Göhring et al., 2010). Vaccination of all horses on the stud farm is in-
dicated; pregnant mares are vaccinated with a booster dose at 5th, 7th and 9th months of pregnancy. It is advised to vaccinate other horses on the breeding premises, starting with a primary course and a second course 4 weeks apart followed by 6-monthly booster vaccination. None of the available vaccines, however, are currently marketed for prevention of EHV-1 neurological disease. In addition, vaccination is complicated by reports of increased risk of EHM (Henninger et al, 2007).

**CONCLUSIONS**

Early detection, treatment and control of EHV-1 and EHV-1 associated manifestations remain a challenge for the equine clinician, as exemplified by the recent outbreaks at riding schools, racetracks and veterinary hospitals worldwide. Implementation of biosafety protocols and control measures is hampered by the potential of early infection and life-long latency. Preventing or at least limiting outbreaks will require educated equine stakeholders and vigilant practitioners with a firm grasp of the disease’s complexity and clinical symptoms.

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**Supplementary Table 1**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Manufacturer (market)</th>
<th>Vaccine type</th>
<th>Protection claim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duvaxyn EHV-1,4</td>
<td>Fort Dodge (Europe)</td>
<td>EHV-1/4, inactivated</td>
<td>Abortion and respiratory disease</td>
</tr>
<tr>
<td>Equiffa</td>
<td>Merial (Europe)</td>
<td>EHV-1, EIV-1 and EIV-2, inactivated</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Equip EHV 1,4</td>
<td>Zoetis (Europe)</td>
<td>EHV1/4, inactivates</td>
<td>Abortion and respiratory disease</td>
</tr>
<tr>
<td>Resequin</td>
<td>Intervet (Europe)</td>
<td>EHV-1 and EHV-4, inactivated</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Resequin Plus</td>
<td>Intervet (Europe)</td>
<td>EHV-1, EHV-4, EIV-1 and EIV-2, inactivated</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Prevaccinol</td>
<td>Intervet (Germany)</td>
<td>EHV-1, modified live RacH strain</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Bioequin H</td>
<td>Bioveta (Europe)</td>
<td>EHV-1, EIV, inactivated</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Fluvac Innovator EHV-1/4</td>
<td>Zoetis LLC (USA)</td>
<td>EHV-1/4, inactivated</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Calvenza 03 EIV/EHV</td>
<td>Boehringer Ingelheim (USA)</td>
<td>EHV-1 -4, EIV type A North American and A2 Eurasian, inactivated vaccine</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Equigard</td>
<td>Boehringer Ingelheim (USA)</td>
<td>EHV-1 and EHV-4, inactivated</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td>EquiVac EHV-1/4</td>
<td>Fort Dodge (USA)</td>
<td>EHV-1 and EHV-4, inactivated</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Fluvac EHV-4/1</td>
<td>Fort Dodge (USA)</td>
<td>EHV-4 and EHV-1, EIV-1, EIV-2, inactivated</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Fluvac Innovator 5</td>
<td>Fort Dodge (USA)</td>
<td>EEV, WEE, EIV, EHV-1/4, tetanus</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Pneumabort K+ 1B</td>
<td>Fort Dodge (USA)</td>
<td>EHV-1, inactivated</td>
<td>Abortion and respiratory disease</td>
</tr>
<tr>
<td>Prestige*</td>
<td>Intervet (USA)</td>
<td>EHV-1/4, inactivated</td>
<td>Respiratory disease</td>
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<tr>
<td>Pneumequine</td>
<td>Boehringer Ingelheim (USA)</td>
<td>EHV-1, inactivated</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Equigard - Flu</td>
<td>Boehringer Ingelheim (USA)</td>
<td>EHV1/4, EIV1, EIV 2, inactivated</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Double E-FT EHV</td>
<td>Fort Dodge (USA)</td>
<td>EHV1/4, EIV1, EIV2, EEEV, WEEV, tetanus, inactivated</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Prodigy</td>
<td>Intervet (USA)</td>
<td>EHV1, inactivated</td>
<td>Abortion</td>
</tr>
<tr>
<td>Rhinomune</td>
<td>Pfizer (USA)</td>
<td>EHV 1, modified live RacH strain</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Rhino-Flu</td>
<td>Pfizer (USA)</td>
<td>EHV-1, modified live EIV1, EIV2, inactivated</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Duvaxyn EHV-1,4</td>
<td>Pfizer (USA)</td>
<td>EHV1/4, inactivated</td>
<td>Respiratory disease</td>
</tr>
</tbody>
</table>

*Abbreviations: EHV, equine herpesvirus; EIV, equine influenza virus types); EEEV, Eastern equine encephalitis virus; WEEV, Western equine encephalitis virus.*


