

# Journal of the Hellenic Veterinary Medical Society

Vol 74, No 2 (2023)



## Equine Herpes Virus-1. A clinician's perspective.

*P Tyrnenopoulou, N Diakakis*

doi: [10.12681/jhvms.29907](https://doi.org/10.12681/jhvms.29907)

Copyright © 2023, P Tyrnenopoulou, N Diakakis



This work is licensed under a [Creative Commons Attribution-NonCommercial 4.0](https://creativecommons.org/licenses/by-nc/4.0/).

### To cite this article:

Tyrnenopoulou, P., & Diakakis, N. (2023). Equine Herpes Virus-1. A clinician's perspective. *Journal of the Hellenic Veterinary Medical Society*, 74(2), 5667–5676. <https://doi.org/10.12681/jhvms.29907> (Original work published July 5, 2023)

## Equine Herpes Virus-1. A clinician's perspective

P. Tyrnenopoulou<sup>1</sup>, N. Diakakis<sup>2</sup>

<sup>1</sup> Assistant Professor, Clinic of Surgery, Faculty of Veterinary Science, School of Health Sciences, University of Thessaly, Greece

<sup>2</sup> Professor, Equine Unit, School of Veterinary Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece

**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

*Corresponding Author:*

Panagiota Tyrnenopoulou, Clinic of Surgery, Faculty of Veterinary Science, School of Health Sciences, University of Thessaly, Greece.  
E-mail address: ptymenop@uth.gr

*Date of initial submission:* 16-03-2022  
*Date of acceptance:* 01-12-2022

## 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 ( $\alpha$ ,  $\beta$ , and  $\gamma$ ) (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 plaque-wise manner in the epithelial cells lining the upper respiratory tract (Gryspeerd 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 (Gryspeerd et al., 2010). In addition, in *in 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 viraemia 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 reactivable, 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 (Bažanów 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 myeloencephalopathy 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 asymptotically 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 bipha-

sic fever, anorexia, lymphadenopathy and oculonasal 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 (Back 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 identify new viruses (cyclovirus, parvoviruses) 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). Peripartum 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., *Strongylus* 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/nasopharyngeal wash and whole-blood buffy-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 log-book 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 1.** Examples of protocols used for the management of equine herpesvirus-1 clinical manifestations

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

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 myeloencephalopathy, corticosteroids may be appropriate, as they limit the degree of thrombo-ischæmic 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 demborexine 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 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-



Supplementary Table 1

## Commercially available equine vaccines for control of disease caused by EHV-1

Vaccine	Manufacturer (market)	Vaccine type	Protection claim
Duvaxyn EHV-1,4	Fort Dodge (Europe)	EHV-1/4, inactivated	Abortion and respiratory disease
Equiffa	Meril (Europe)	EHV-1, EIV-1 and EIV-2, inactivated	Respiratory disease
Equip EHV 1,4	Zoetis (Europe)	EHV1/4, inactivates	Abortion and respiratory disease
Resequin	Intervet (Europe)	EHV-1 and EHV-4, inactivated	Respiratory disease
Resequin Plus	Intervet (Europe)	EHV-1, EHV-4, EIV-1 and EIV-2, inactivated	Respiratory disease
Prevaccinol	Intervet (Germany)	EHV-1, modified live RacH strain	Respiratory disease
Bioequin H	Bioveta (Europe)	EHV-1, EIV, inactivated	Respiratory disease
Fluvac Innovator EHV-1/4	Zoetis LLC (USA)	EHV-1/4, inactivated	Respiratory disease
Calvenza 03 EIV/EHV	Boehringer Ingelheim (USA)	EHV-1 -4, EIV type A2 North American and A2 Eurasian, inactivated vaccine	Respiratory disease
Equigard	Boehringer Ingelheim (USA)	EHV-1 and EHV-4, inactivated	Respiratory disease
EquiVac EHV-1/4	Fort Dodge (USA)	EHV-1 and EHV-4, inactivated	Respiratory disease
Fluvac EHV4/1	Fort Dodge (USA)	EHV-4 and EHV-1, EIV-1, EIV-2, inactivated	Respiratory disease
Fluvac Innovator 5	Fort Dodge (USA)	EEV, WEE, EIV, EHV-1/4, tetanus	Respiratory disease
Pneumabort K+ 1B	Fort Dodge (USA)	EHV-1, inactivated	Abortion and respiratory disease
Prestige*	Intervet (USA)	EHV-1/4, inactivated	Respiratory disease
Pneumequine	Boehringer Ingelheim (USA)	EHV-1, inactivated	Respiratory disease
Equigard - Flu	Boehringer Ingelheim (USA)	EHV1/4, EIV1, EIV 2, inactivated	Respiratory disease
Double E-FT EHV	Fort Dodge (USA)	EHV1/4, EIV1, EIV2, EEEV, WEEV, tetanus, inactivated	Respiratory disease
Prodigy	Intervet (USA)	EHV1, inactivated	Abortion
Rhinomune	Pfizer (USA)	EHV 1, modified live RacH strain	Respiratory disease
Rhino-Flu	Pfizer (USA)	EHV-1, modified live EIV1, EIV2, inactivated	Respiratory disease
Duvaxyn EHV-1,4	Pfizer (USA)	EHV1/4, inactivated	Respiratory disease

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

icated; 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 biosecurity 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.

## REFERENCES

- Allen GP (2008) Risk factors for development of neurologic disease after experimental exposure to equine herpesvirus-1 in horses. *Am J Vet Res* 69(12):1595-1600.
- Allen GP, Kydd JH, Slater JD and Smith KC (2004) Equid herpesvirus 1 (EHV-1) and equid herpesvirus 4 (EHV-4) infections In: *Infectious Diseases of Livestock*, Eds: J.A.W. Coetzer and R.C. Tustin, Oxford Press, Cape Town: pp 829-859.
- Altan E, Li Y, Sabino-Santos Jr G, Sawaswong V, Barnum S, Pusterla N, Deng X, Delwart E (2019) Viruses in horses with neurologic and respiratory diseases. *Viruses* 11(10): 942
- Autio K, Rassnick KM, Bedford-Gauas SJ (2007) Chemotherapy during pregnancy: a review of the literature. *Vet Comp Oncol* 5:61-75.
- Back H, Weld J, Walsh C, Cullinane A (2019) Equine Rhinitis A Virus Infection in Thoroughbred Racehorses—A Putative Role in Poor Performance?. *Viruses* 11(10): 963.
- Balasuriya UB, Carossino M, Timoney PJ (2008). Equine viral arteritis: a respiratory and reproductive disease of significant economic importance to the equine industry. *Equine Vet Educ* 30(9):497-512.
- Barba M, Fairbanks EL, Daly JM (2019) Equine viral encephalitis: prevalence, impact, and management strategies. *Vet Med: Research and Reports Vet Med (Auckl)* 10:99.
- Bazanow BA, Fracka AB, Jackulak NA, Staroniewicz ZM, Ploch SM (2014) A 34-year retrospective study of equine viral abortion in Poland *Pol J Vet Sci* 17:607-12.
- Boyle AG, Timoney JF, Newton JR, Hines MT, Waller AS, Buchanan BR (2018) Streptococcus equi infections in horses: guidelines for treatment, control, and prevention of strangles—revised consensus statement. *J Vet Intern Med* 32(2):633-47.
- Bryant NA, Wilkie GS, Russell CA, Compston L, Grafham D, Clissold L, McLay K, Medcalf L, Newton R, Davison AJ, Elton DM (2018) Genetic diversity of equine herpesvirus 1 isolated from neurological, abortigenic and respiratory disease outbreaks *Transbound Emerg Dis* 65(3):817-32.
- Burgess BA, Tokatelloff N, Manning S, Lohmann K, Lunn DP, Hussey SB, Morley PS (2012) Nasal Shedding of Equine Herpesvirus-1 from Horses in an Outbreak of Equine Herpes Myeloencephalopathy in Western Canada. *J Vet Intern Med* 26(2):384-92.
- Burrows R and Goodridge D (1973) In vivo and in vitro studies of equine rhinopneumonitis strains In *Equine Infectious Diseases III*, pp. 306-321 Eds. J. T. Bryans and H. Gerber Karger, Basel.
- Carmichael RJ, Whitfield C, Maxwell LK (2013) Pharmacokinetics of ganciclovir and valganciclovir in the adult horse. *J Vet Pharmacol Ther* 36(5):441-9. doi: 10.1111/jvp.12029
- Castro ER, Arbiza J (2017) Detection and genotyping of equid herpesvirus 1 in Uruguay. *Rev Sci Tech* 36:799-806.
- Crabb BS, Studdert MJ (1993) Epitopes of glycoprotein G of equine herpesviruses 4 and 1 located near the C termini elicit type-specific antibody responses in the natural host. *J Virol* 67(10):6332-8.
- Damiani AM, de Vries M, Reimers G, Winkler S, Osterrieder N (2014) A severe equine herpesvirus type 1 (EHV-1) abortion outbreak caused by a neuropathogenic strain at a breeding farm in northern Germany. *Vet Microbiol* 172(3-4):555-562.
- Davison AJ, Eberle R, Ehlers B, Hayward GS, McGeoch DJ, Minson AC, Pellett PE, Roizman B, Studdert MJ, Thiry E (2009) The order herpesvirales. *Archives of virology* 154(1):171-7.
- Dimock WW (1940) The diagnosis of virus abortion in mares *J Am Vet Med Assoc* 96, 665-666.
- Dimock WW, Edwards PR (1933) Is there a filterable virus of abortion in mares? *Ky Agric Exp Stn Bull* 333:291-301.
- Dixon RJ, Hartley WJ, Hutchins DR, Lephed EE, Feilen C, Jones RF, Love DN, Sabine M, Wells AL (1978) Perinatal foal mortality associated with a herpesvirus. *Aus Vet Journal* 54(3):103-5.
- Edington N, Bridges CG, Huckle A (1985). Experimental reactivation of equid herpesvirus 1 (EHV 1) following the administration of corticosteroids. *Equine Vet J*. 17(5):369-72.
- Equine Disease Communication Center (EDCC) (2021) <https://www.equine-diseasecc.org/alerts> [accessed 12 May 2021]
- Fédération Equestre Internationale (FEI) (2021) <https://inside.fei.org/fei/ehv-1> [accessed 11 May 2021]
- Garré B, Gryspeerdt A, Croubels S, De Backer P, Nauwynck H (2009) Evaluation of orally administered valacyclovir in experimentally EHV-1 infected ponies. *Vet Microbiol* 135 (3-4):214-21.
- Gerst S, Borchers K, Gower SM, Smith KC (2003) Detection of EHV-1 and EHV-4 in placental sections of naturally occurring EHV-1-and EHV-4-related abortions in the UK: use of the placenta in diagnosis. *Equine Vet J* 35(5):430-3.
- Gibson JS, Slater JD, Awan AR, Field HJ (1992) Pathogenesis of equine herpesvirus-1 in specific pathogen-free foals: primary and secondary infections and reactivation. *Arch Virol* 1;123:351-66.
- Gibson JS, Slater JD, Field HJ (1992) The pathogenicity of Ab4p, the sequenced strain of equine herpesvirus-1, in specific pathogen-free foals *Virol* 1;189(1):317-9.
- Gilger BC (2010) Equine recurrent uveitis: the viewpoint from the USA. *Equine Vet J* 2010 42(S37):57-61.
- Gilkerson JR, Bailey KE, Diaz-Méndez A, Hartley CA (2015) Update on viral diseases of the equine respiratory tract. *Vet Clin: Equine Pract* 31(1):91-104.
- Gilkerson JR, Love DN, Whalley JM (2000) Incidence of equine herpesvirus 1 infection in Thoroughbred weanlings on two stud farms *Aust Vet J* 78(4):277-8.
- Göhring LS, Brandes K, Ashton LV, Wittenburg LA, Olea-Popelka FJ, Lunn DP, Soboll Hussey G (2017) Anti-inflammatory drugs decrease infection of brain endothelial cells with EHV-1 in vitro. *Equine Vet J* 49(5):629-36.
- Göhring LS, Landolt GA, Morley PS (2010) Detection and management of an outbreak of equine herpesvirus type 1 infection and associated neurological disease in a veterinary teaching hospital. *J Vet Intern Med* 24(5):1176-83.
- Göhring LS, Van Maanen C, van Oldruitenborgh-Oosterbaan MS (2005) Neurological syndromes among horses in The Netherlands a 5 year retrospective survey (1999-2004). *Vet Q* 27(1):11-20.
- Griffith RS, Walsh DE, Myrmel KH, Thompson RW, Behforooz A (1987) Success of L-lysine therapy in frequently recurrent herpes simplex infection. *Dermatology* 175(4):183-90.
- Grinde B (2013) Herpesviruses: latency and reactivation - viral strategies and host response *J Oral Microbiol* 5:10.3402/jom.v3405i3400.22766 doi: 10.3402/jom.v3405i3400.22766.
- Gryspeerdt AC, Vandekerckhove AP, Garré B, Barbé F, Van de Walle GR, Nauwynck HJ (2010) Differences in replication kinetics and cell tropism between neurovirulent and non-neurovirulent EHV1 strains during the acute phase of infection in horses. *Veterinary microbiology* 142(3-4):242-53.
- Hartley CA, Dynon KJ, Mekuria ZH, El-Hage CM, Holloway SA, Gilkerson JR (2013) Equine gammaherpesviruses: perfect parasites? *Vet Microbiol* 167(1-2):86-92.
- Hartley CA, Wilks CR, Studdert MJ, Gilkerson JR (2005) Comparison of antibody detection assays for the diagnosis of equine herpesvirus 1 and 4 infections in horses. *Am J Vet Res* 66(5):921-8.
- Henninger RW, Reed SM, Saville WJ, Allen GP, Hass GF, Kohn CW, Sofaly C (2007). Outbreak of neurologic disease caused by equine herpesvirus-1 at a university equestrian center. *J Vet Intern Med* 21, 157-165.
- Hernandez D, Yeo WM, Brooks MB, Ness SL, Divers TJ, Stokol T (2016) Effects of various antiplatelet drugs on ex vivo platelet activation induced by equine herpesvirus type 1. *Am J Vet Res* 77(12):1366-73.
- Hussey GS, Goehring LS, Lunn DP, Hussey SB, Huang T, Osterrieder N, Powell C, Hand J, Holz C, Slater J (2013) Experimental infection with equine herpesvirus type 1 (EHV-1) induces chorioretinal lesions. *Vet Res* 44(1):1-5.
- Hussey SB, Clark R, Lunn KF, Breathnach C, Soboll G, Whalley JM, Lunn DP (2006) Detection and quantification of equine herpesvirus-1 viremia and nasal shedding by real-time polymerase chain reaction. *J Vet Diagn Invest* 18(4):335-42.
- Ivens P (2014) EHM—What every equine practitioner needs to know. *Livest* 19(3):180-5.
- Karlin S, Mocarski ES, Schachtel GA (1994) Molecular evolution of herpesviruses: genomic and protein sequence comparisons. *Journal of virology* 68(3):1886-902.
- Khusro A, Aarti C, Rivas-Caceres RR, Barbabosa-Pliego A (2020) Equine herpesvirus-1 infection in horses: Recent updates on its pathogenicity, vaccination, and preventive management strategies. *J Equine V Sci* 87:102923.
- Kress F (1941) Virus abortus bei der Stute, Wien *Tieraerztl Wochenschr* 28:320.
- Kydd JH, Slater J, Osterrieder N, Lunn DP, Antczak DF, Azab W, Balasuriya U, Barnett C, Brosnahan M, Cook C, Damiani A (2012) Third international havemeyer workshop on equine herpesvirus type 1. *Equine Vet J*. 44(5):513-7.

- Kydd JH, Townsend HG, Hannant D (2006) The equine immune response to equine herpesvirus-1: the virus and its vaccines. *Vet Immunol Immunopathol* 111(1-2):15-30.
- Laval K, Poelaert KC, Van Cleemput J, Zhao J, Vandekerckhove AP, Gryspeerdt AC, Garré B, van der Meulen K, Baghi HB, Dubale HN, Zarak I (2021) The Pathogenesis and Immune Evasive Mechanisms of Equine Herpesvirus Type 1. *Frontiers in Microbiology* Mar 4;12:435.
- Lecollinet S, Pronost S, Couplier M, Beck C, Gonzalez G, Leblond A, Tritz P (2020) Viral equine encephalitis, a growing threat to the horse population in Europe?. *Viruses* 12(1):23.
- Long MT (2014) West Nile virus and equine encephalitis viruses: new perspectives. *Vet Clin Equine* 30(3):523-42.
- Lunn DP, Davis-Poynter N, Flaminio MJ, Horohov DW, Osterrieder K, Pusterla N, Townsend HG (2009) Equine herpesvirus-1 consensus statement. *J Vet Intern Med.* 23(3):450-61. doi: 10.1111/j.1939-1676.2009.0304.x. PMID: 19645832.
- Ma G, Azab W, Osterrieder N (2013) Equine herpesviruses type 1 (EHV-1) and 4 (EHV-4)—masters of co-evolution and a constant threat to equids and beyond *Vet microbiol* 29;167(1-2):123-34.
- Mailoo VJ, Rampes. S (2017) Lysine for herpes simplex prophylaxis. *Integr Med* 16(3):42-46.
- Manninger R, Csontos J (1941) Virusabortus der Stuten. *Dtsch Tierarztl Wschr* 49:105-11.
- Marenzoni ML, Lepri E, Proietti PC, Bietta A, Coletti M, Timoney PJ, Pasamonti F. (2012) Causes of equine abortion, stillbirth and neonatal death in central Italy. *The Vet Rec* 170(10):262.
- Maxwell LK, Bentz BG, Bourne DW, et al (2008) Pharmacokinetics of valacyclovir in the adult horse. *J Vet Pharmacol Ther* 31:312–20
- McCann SH, Mumford JA, Binns MM (1995) Development of PCR assays to detect genetic variation amongst equine herpesvirus-1 isolates as an aid to epidemiological investigation. *J Virol Methods* 52(1-2):183-94.
- McCartan CG, Russell MM, Wood JL, Mumford JA (1995) Clinical, serological and virological characteristics of an outbreak of paresis and neonatal foal disease due to equine herpesvirus-1 on a stud farm. *Vet Rec* 136(1):7-12.
- McFadden AM, Hanlon D, McKenzie RK, Gibson I, Bueno IM, Pulford DJ, Orr D, Dunowska M, Stanislawek WL, Spence RP, McDonald WL, Munro G, Mayhew IG (2016) The first reported outbreak of equine herpesvirus myeloencephalopathy in New Zealand. *N Z Vet J* 64(2):125-34. doi: 10.1080/00480169.2015.1096853.
- Mesquita LP, Costa RC, Mesquita LL, Lara MD, Villalobos EM, Mori CM, Mori E, Howarth EW, Maiorka PC (2021) Pathogenesis of Equid Alpha-herpesvirus 1 Infection in the Central Nervous System of Mice. *Vet Path* 15:03009858211020670.
- Negussie H, Gizaw D, Tessema TS, Nauwynck HJ (2017) Equine herpesvirus-1 myeloencephalopathy, an emerging threat of working equids in ethiopia. *Transbound Emerging Dis* 64(2):389-97.
- O'Callaghan DJ, Osterrieder N (2008) Herpesviruses of horses. In: *Encyclopedia of Virology*. 3rd ed, Academic Press, New York :pp 411-420
- Oladunni FS, Horohov DW, Chambers TM (2019) EHV-1: A constant threat to the horse industry *Front Microbiol* 3;10:2668.
- Osterrieder N, Van de Walle GR (2010) Pathogenic potential of equine alpha-herpesviruses: the importance of the mononuclear cell compartment in disease outcome. *Vet microbiol* 16;143(1):21-8.
- Paillot R, Marcillaud Pitel C, D'ablon X, Pronost S (2016) Equine Vaccines: How, When and Why? Report of the vaccinology session, french equine veterinarians association, Reims.
- Paillot R, Sutton G, Thieulent C, Marcillaud-Pitel C; Pronost S (2020) New EHV-1 variant identified *Vet Rec* 186, 573.
- Payne S (2017) Family Hepeviridae. *Viruses MDPI*: Basel, Switzerland 121-4.
- Preziuso S, Sgorbini M, Marmorini P, Cuteri V (2019) Equid alphaherpesvirus 1 from Italian Horses: Evaluation of the Variability of the ORF30, ORF33, ORF34 and ORF68 Genes. *Viruses* 11(9):851.
- Pronost S, Cook RF, Fortier G, Timoney PJ, Balasuriya UB (2010) Relationship between equine herpesvirus-1 myeloencephalopathy and viral genotype. *Equine Vet J* 42(8):672-4.
- Pusterla N, Barnum S, Miller J, Varnell S, Dallap-Schaer B, Aceto H, Simeone A (2021) Investigation of an EHV-1 outbreak in the United States caused by a new H752 genotype *Pathogens* 10(6):747.
- Pusterla N, Hussey GS. Equine herpesvirus 1 myeloencephalopathy (2014) *Vet Clin North Am Equine Pract* (2014) 30(3):489-506. doi: 10.1016/j.cveq.2014.08.006. Epub 2014 Oct 7. PMID: 25300635.
- Randall CC, Ryden FW, Doll ER & Schell FS (1953) *Amer Jour Path* 29, 139.
- Roizman B (1991) Family Herpesviridae. In: Francki RIB, Fauquet CM, Knudson DL and Brown F (eds) *Classification and nomenclature of viruses*. 5th Report of the International Committee on Taxonomy of Viruses Arch *Viral.*, 2 (suppl) :103-110.
- Saxegaard F (1966) Isolation and identification of equine rhinopneumonitis virus (equine abortion virus) from cases of abortion and paralysis *Nord Vet Med* 18:504-12.
- Schulman ML, Kass PH, Becker A, Van der Merwe B (2013) A predictive model for reproductive performance following abortion in Thoroughbred mares *Vet Rec* 172(2):44.
- Shiraki K (2018) Antiviral drugs against alphaherpesvirus. *Adv Exp Med Biol* 1045: 103–122.
- Slater J (2007) Equine herpesviruses. In: *Equine Infectious Diseases*. Saunders Elsevier, St. Louis, Missouri, USA: pp 134–153.
- Smith KC, Blunden AS, Whitwell KE, Dunn KA, Wales AD (2003) A survey of equine abortion, stillbirth and neonatal death in the UK from 1988 to 1997 *Equine Vet J* 35(5):496-501
- Smith KL, Li Y, Breheny P, Cook RF, Henney PJ, Sells S, Pronost S, Lu Z, Crossley BM, Timoney PJ, Balasuriya UB (2012) New real-time PCR assay using allelic discrimination for detection and differentiation of equine herpesvirus-1 strains with A2254 and G2254 polymorphisms. *J Clin Microbiol* 50(6):1981-8.
- Stasiak K, Dunowska M, Rola J (2020) Outbreak of equid herpesvirus 1 abortions at the Arabian stud in Poland. *BMC Vet Res* 16(1):1-8.
- Stokol T, Serpa PBS, Zahid MN, Brooks MB (2016) Unfractionated and low-molecular-weight heparin and the phosphodiesterase inhibitors, IBMX and cilostazol, block ex vivo equid herpesvirus type-1-induced platelet activation. *Front Vet Sci* 3:99. doi: 10.3389/fvets.2016.00099.
- Studdert MJ, Hartley CA, Dynon K, Sandy JR, Slocombe RR, Charles JA, Milne ME, Clarke AF, El-Hage C (2003) Outbreak of equine herpesvirus type 1 myeloencephalitis: new insights from virus identification by PCR and the application of an EHV-1-specific antibody detection ELISA. *Vet Rec* 153(14):417-23.
- Sutton G, Thieulent C, Fortier C, Hue ES, Marcillaud-Pitel C, Pléau A, Deslis A, Guitten E, Paillot R, Pronost S (2020) Identification of a New Equid Herpesvirus 1 DNA Polymerase (ORF30) Genotype with the Isolation of a C2254/H752 Strain in French Horses Showing no Major Impact on the Strain Behaviour *Viruses* 12(10):1160.
- Telford EA, Watson MS, Perry J, Cullinane AA, Davison AJ (1998) The DNA sequence of equine herpesvirus-4. *J Gen Virol* 79(5):1197-203.
- Traub-Dargatz JL, Pelzel-McCluskey AM, Creekmore LH, Geiser-Novotny S, Kasari TR, Wiedenheft AM, Bush EJ, Bjork KE (2013) Case-control study of a multistate equine herpesvirus myeloencephalopathy outbreak. *J Vet Intern Med* 27(2):339-46.
- Van Cleemput J, Poelaert KC, Laval K, Maes R, Hussey GS, Van den Broeck W, Nauwynck HJ (2017) Access to a main alphaherpesvirus receptor, located basolaterally in the respiratory epithelium, is masked by intercellular junctions. *Sci Rep* 30;7(1):1-5.
- Van den Ingh TS, Binkhorst GJ, Kimman TG, Vreeswijk J, Pol JM, Van Oirschot JT (1990) Aujeszky's disease in a horse. *J Vet Med Series B* 37(1-10):532-8.
- Van Maanen C, van Oldruitenborgh-Oosterbaan MS, Damen EA, Derksen AG (2001) Neurological disease associated with EHV-1-infection in a riding school: clinical and virological characteristics. *Equine Vet J* 2001 33(2):191-196.
- Van Maanen C, Willink DL, Smeenk LA, Brinkhof J, Terpstra C. An equine herpesvirus 1 (EHV1) abortion storm at a riding school (2000) *Vet Q* 1;22(2):83-7.
- Vandekerckhove A, Glorieux S, Gryspeerdt A, Steukers L, Duchateau L, Osterrieder N, Van de Walle G, Nauwynck H (2010) Replication kinetics of neurovirulent versus non-neurovirulent equine herpesvirus type 1 strains in equine nasal mucosal explants. *Journal of General Virology* 91(8):2019-28.
- Vautmans H, European Parliament (2021) [https://www.europarl.europa.eu/doceo/document/P-9-2021-001223\\_EN.html](https://www.europarl.europa.eu/doceo/document/P-9-2021-001223_EN.html) [accessed 26 May 2021]
- Walter J, Seeh C, Fey K, Bleul U, Osterrieder N (2013) Clinical observations and management of a severe equine herpesvirus type 1 outbreak with abortion and encephalomyelitis. *Acta Vet Scand* 55(1):1-9.
- Walter J, Seeh C, Fey K, Bleul U, Osterrieder N (2013) Clinical observations and management of a severe equine herpesvirus type 1 outbreak with abortion and encephalomyelitis. *Acta Vet Scand* 55(1):19. doi: 10.1186/1751-0147-55-19. PMID: 23497661; PMCID: PMC3630004.
- Westerfield C, Dimock WW (1946) The pathology of equine virus abortion. *Journal of the American Veterinary Medical Association* 109:101-11.
- Wilson WD (1997) Equine herpesvirus 1 myeloencephalopathy *Vet Clin North Am Equine Pract* 13: 53–72.
- Xie J, Tong P, Zhang L, Ren M, Song X, Jia C, Palidan N, Zhang L, Kuang L (2021) First detection and genetic characterization of equid herpesvirus 2, 4, and 5 in China. *Arch Virol* 166(5):1421-6.