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An overview of Equine Herpesviruses with special regard to the 2021 spring EHV-1 outbreak in Europe.

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Table of Content

Abbreviation

ACV	Acyclovir
AGID	Agar Gel Immunodiffusion Assay
BC	buffy coat
BSC-1	Standards-Cercopithecus-1
CF	complement fixation
CFT	complement fixation test
CNS	central nervous system
CSF	cerebrospinal fluid
CSPH	chondroitin sulfate proteoglycans
DNA	Deoxyribonucleic acid
ECE	equine coital exanthema
EHV	equine herpesvirus
EHM	equine herpes myeloencephalopathy
ELISA	Enzyme-linked Immuno Sorbent Assay
EMPF	equine multinodular pulmonary fibrosis
EMS	equine myeloencephalitis
FEI	Fédération Équestre Internationale
FN	Deutsche Reiterlicher Vereinigung
g	glycoprotein
gB	glycoprotein B
GCV	Ganciclovir
gC	glycoprotein C
gD	glycoprotein D
gE	glycoprotein E
gG	glycoprotein G
gH	glycoprotein H
gI	glycoprotein I
gK	glycoprotein K
gL	glycoprotein L
gM	glycoprotein M
gN	glycoprotein N

HSPG	heparan sulfate proteoglycans
IE	immediate early proteins
IF	immunofluorescence
Ihc	immunohistochemistry
LAT	Latency Associated Transcripts
MHC-1	major histocompatibility complex I
mm	millimeters
MSD	Merck Sharp & Dohme
nm	nanometer
NS	nasal swab
NSAID	non-steroidal anti-inflammatory drugs
OIE	Office International des Epizooties
PBL	peripheral blood Lymphocytes
PBMC	Peripheral blood mononuclear cells
PCR	polymerase chain reaction
RK	rabbit kidney
RNA	Ribonucleic acid
RP	relative potency
RT	real-time
TCID50	tissue culture infectious dosis 50%
USA	United States of America
VI	virus isolation
VNI	virus neutralization index
VN	virus neutralization

1 Introduction

The equine herpesviruses (EHV) are a group of pathogens that have long been of concern to the equine industry and veterinary medicine due to their ability to cause a wide range of clinical manifestations and significant economic losses. The year 2021 witnessed a notable and alarming outbreak of EHV-1 in Valencia, Spain. This outbreak highlighted the urgency of understanding the biology, epidemiology, and management of these viruses, as well as the wider implications for equine health, welfare, and the equine industry.

Equine herpesviruses, which belong to the *Herpesviridae* family, include several subtypes, of which EHV-1 and EHV-4 are the most implicated in equine disease. The clinical spectrum associated with EHV infection is broad and includes respiratory disease, abortion in pregnant mares and potentially fatal neurological disease. These findings underscore the profound impact that EHV can have on equine health and the economic sustainability of the industry.

The 2021 outbreak in Valencia is a clear reminder of the pervasive nature of EHV and its potential for devastating consequences. This event attracted global attention due to its rapid spread, affecting a wide range of horses and the international equestrian sport. It highlighted the challenges of managing EHV outbreaks in the context of international horse transport, equestrian sport and animal keeping. The Valencia outbreak serves as a case study that encapsulates the complexities and vulnerabilities associated with EHV control and calls for a more comprehensive examination of this virus and its management strategies.

This thesis aims to provide an understanding of equine herpesviruses in general, their virology, pathogenesis, clinical presentation, transmission dynamics and control measures. It will also analyze the Valencia outbreak in detail. This research will provide valuable insights and lessons learned to inform better strategies for the prevention and management of EHV in the equine industry, ultimately contributing to the advancement of equine health and welfare.

2 EHV-General

2.1 Aetiology

2.1.1 Classification

Equine herpesviruses are members of the *Herpesviridae* family of viruses. The family comprises over a hundred viruses, that can infect a wide range of hosts such as amphibians, reptiles, fish, birds, and mammals, including humans [1] [2] [3].

Due to the vast array of viruses within the *Herpesviridae* family, their classification is of great complexity, starting with the division of the family into three subfamilies (*Alphaherpesvirinae*, *Betaherpesvirinae*, *Gammaherpesvirinae*) [1] [4] .

These subfamilies are each subordinated to several other genera (**Fig.1**.). To date, there are nine known equine herpesvirus species, EHV-1, EHV-2, EHV-3, EHV-4, EHV-5, EHV-6, EHV-7, EHV-8, EHV-9. The EHV-1, -3-,4-,6-,8-,9 belongs to the *Alphaherpesvirinae* subfamily. The EHV-2, -5, -7, belongs to the *Gammaherpesvirinae* family. Of these nine subgroups, only EHV-1, -2, -3, -4 can cause a disease in horses [5] [6] .

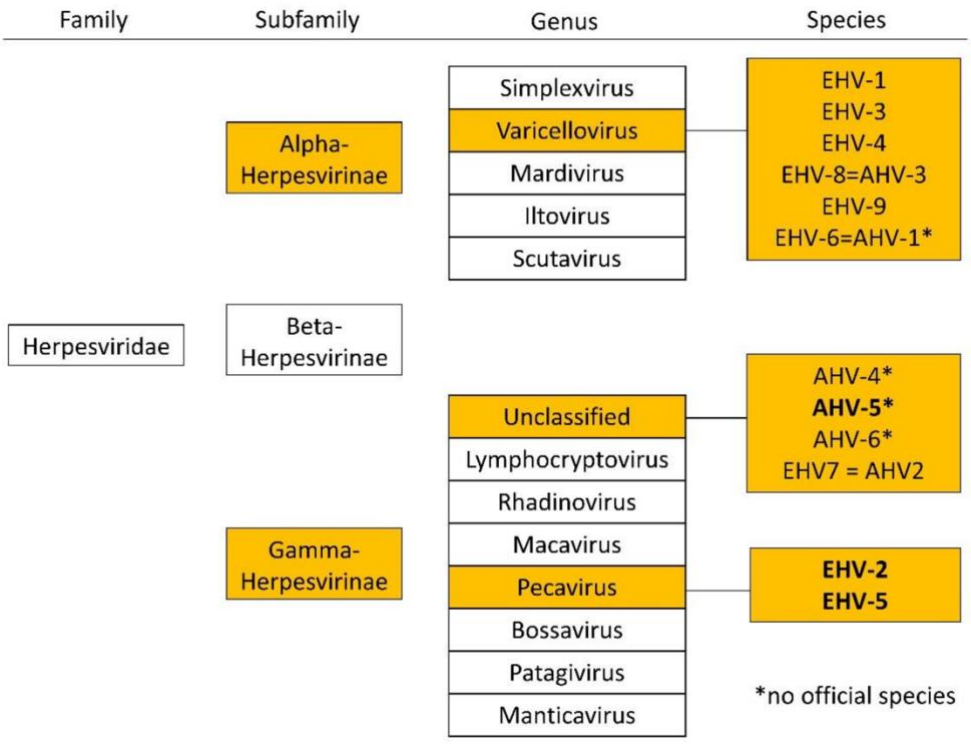

Figure 1: Taxonomy of EHV [7]

EHV-1 belongs to the genus *Varicellovirus*, which is responsible for causing a range of clinical conditions in horses. These diseases can be as severe as neurological infections, which can be fatal in 50 % of the infected equids, such as the equine herpes myeloencephalopathy (EHM), and lead to significant economic losses. Besides this, there are also milder or subclinical infections which leads to abortion and respiratory signs such as the equine rhinopneumonitis [5] [8] [9] [10].

EHV-2 belongs to the genus named *Pecavirus.* It is closely related to EHV-5 which belongs to the same genus and is reportedly present in horse populations worldwide [11] [12]. This virus is associated with mild respiratory diseases, mainly in young animals, such as pharyngitis, lymphadenopathy and pyrexia or rhinitis. The EHV-2 virus is associated with the pathogenesis of keratoconjunctivitis in young horses and the EHV-5 is associated with the epidemiology of pulmonary nodular fibroses in adult horses [13] [14] [15] [16].
The EHV-3 belongs to the genus named *Varicellovirus,* it is the causative agent of equine coital exanthema (ECE), which is a disease occurring worldwide [17] [18].
The EHV-4 also belongs to the genus named *Varicellovirus.* It is a widely acknowledged respiratory pathogen that causes tracheobronchitis and rhinopharyngitis. Besides, it is also associated with sporadic abortions [19] [1] [20].

2.1.2 Virus Structure

Herpesviruses differ morphologically from all other viruses. Their structure is complex, comprised of an outer lipid envelope surrounding an icosahedral capsid (**Fig.2)**. The icosahedral capsid surrounds the double-stranded Deoxyribonucleic acid (DNA) with a proteinaceous matrix. Between the envelope and the capsid, a Tegument is formed. The viral capsid is 100 – 110 nanometer (nm) in diameter. The envelope contains of around twelve different glycoproteins (g), these are gB, gC, gD, gE, gG, gH, gI, gK, gL, gM, gN and gp2. These glycoproteins are necessary for some cell related processes, such as virus attachment, cell-to-cell spread and egress [21] [22] [23].

Concerning virus attachment, glycoprotein D binds to the host cell entry receptors, with the help of the glycoprotein C, which is essential for the initial attachment to the host cells surface proteoglycans, as it also inhibits the host cell complement cascade activation, effectively preventing the host immune reaction. Another part of the attachment to the cell is glycoprotein B, as it forms spikes on the surface of the virion envelope and is thus essential for the initial attachment to the heparin sulfate moieties of the host cell surface [24] [25] [26].

Continuing with the entry of the virion into the cell, glycoprotein H is required, to form a heterodimer with glycoprotein-L (gH/gL). Glycoprotein M helps the correct absorption into the cell. As gM requires gN for a proper maturation, gM directs gN to the Golgi-network of the host. Glycoprotein K modulates membrane fusion events [27] [28][29] [30] [31].

For the cell to cell spread, glycoproteins gE and gI are necessary, as they form a heterodimer. By sorting incipient virions to the cell junctions, the virus spreads to contiguous cells.
For the inhibition of the chemotaxis of host neutrophils, glycoprotein G forms a chemokine-binding protein [32] [33] [34] [35] [36] [37].

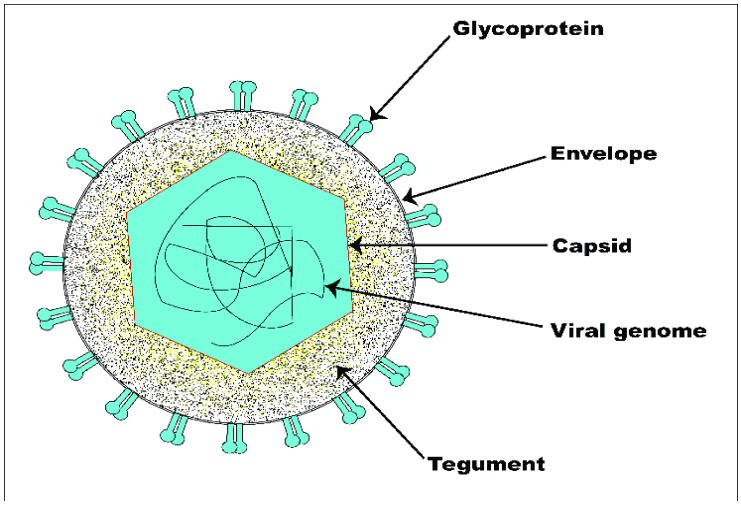

Figure 2: Structure of Herpesvirus virions [8]

2.1.3 Pathogenesis

The pathogenesis of EHV viruses is studied very thoroughly in horses, and slightly differs between the different genera of the *Herpesviridae* family [38] [39] [40]. In general, the host is infected by the virus containing secretes of an infected horse. These viruses, mostly transmitted as an airborne infection (or are activated due to the reactivation of latency), reach the upper respiratory tract mucosa, and from there the regional lymph nodes, where the primary replication starts [41] [38] [42]

The lytic infection starts with the EHV binding to the host cells cell surface HSPG (Heparan Sulfate Proteoglycan) and CSPG (Chondroitin Sulfate Proteoglycan), supported by gC and gB and leads to the attachment of the virus to the host cell. MHC-1 (Major Histocompatibility Complex -1) is activated and functions as an entry receptor while binding to gD, this process leads to the fusion of the virus into the cell [8] [43] [44] [45] [46].

The fusion happens due the amalgamation of the virus envelope and the plasma membrane of the host cell. After the fusion, the virus capsid migrates to the nucleus with the help of microtubules. The nucleus is the site of viral replication. The newly replicated DNAs are incorporated into newly assembled nucleocapsids, which allows the virus particle to migrate through the nuclear membrane, where another fusion process generated the primary envelope and then the virus continues its journey to the outer cell membrane. Then newly formed nucleocapsids get released from the cell through exocytosis [8] [47] [48] [49].

The virus causes erosions and necrosis of the epithelial cells and viral shedding in the environment begins. The virus continues to penetrate the deeper layers of the epithelium, the lamina propria, infecting PBMC (Peripheral Blood Mononuclear Cells), and using these to disseminate through the whole body, leading to a viraemia. A second process of infection route occurring at the same time, is the infection of the neurons of the trigeminal nerves. This happens in the first 48 hours post infection and may lead to a latent infection [50] [38] [8] [40] [10].

The viral pathogenesis continues with a systemic and cell associated viraemia, spreading the virus all over the body to the target organs, such as to the uterus, causing abortion in case of EHV-1 and less frequently of EHV-4. Furthermore, viraemia leads to ischemic thrombi and

vasculitis. Monocytes, T cells, and B cells are the main cell types infected during the cell-associated viraemia [42] [38] [10] [8] [40].

Main aspects of the Pathogenesis are shown in **Figure 3.**:

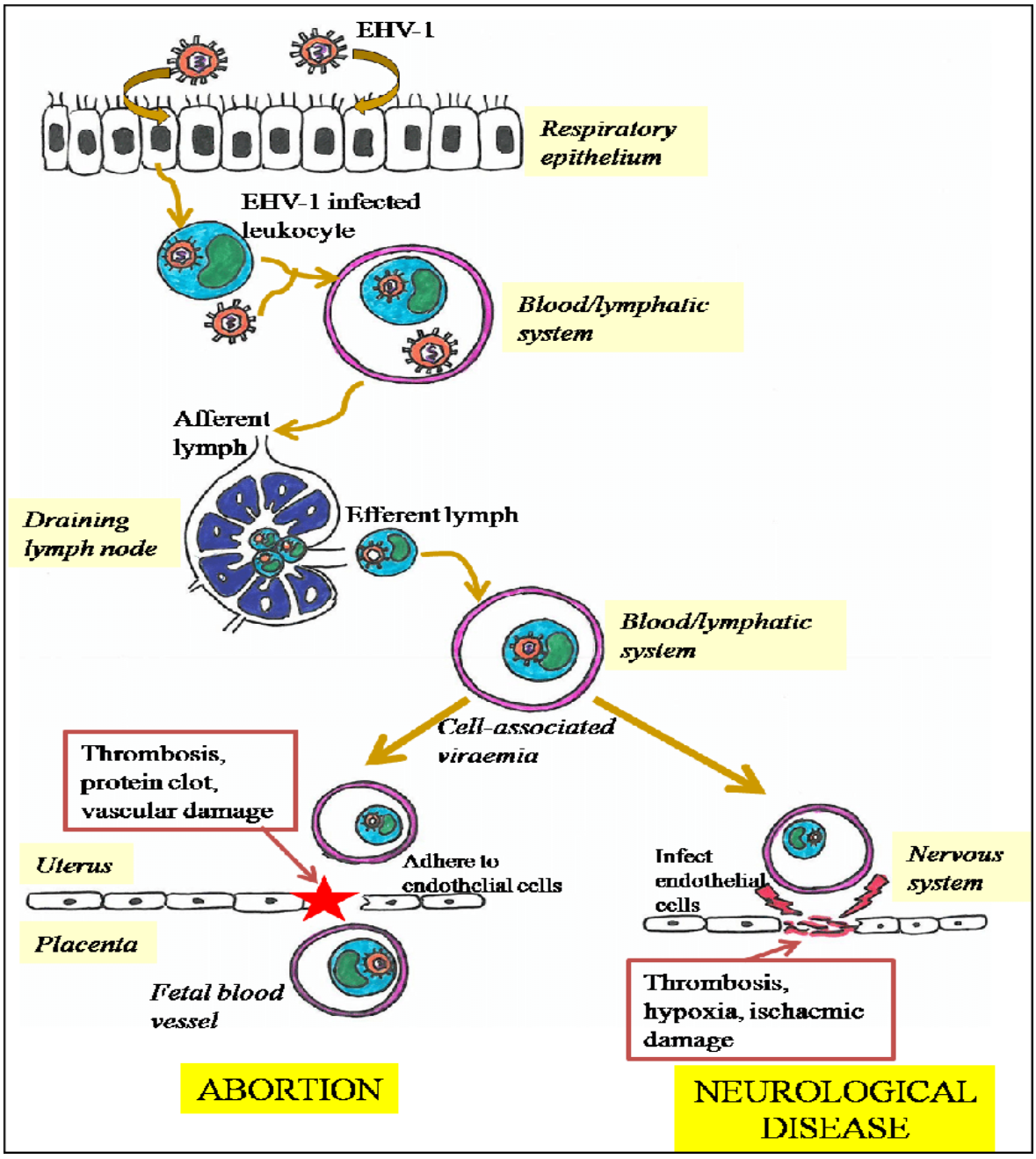

Figure 3: The pathogenesis of EHV-1 [51].

A difference in the pathogenesis is seen at EHV-3 infection, starting with a possible different route of infection, the venereal transmission. EHV-3 replicates in the epithelia of mucocutaneous margins and skin in the stratified epithelium. The lytic infection of the

epithelial cells leads to their lysis and elicits a localized inflammatory response, leading to the characteristic skin lesions of ECE [52] [40] [53] [54].

2.2 Epidemiology

2.2.1 History

The initial record of the EHV viruses, dates to the University of Kentucky Agricultural Experiment Station in Lexigton, KY, in 1932, when the EHV-1 virus was identified as "equine abortion virus" [55] [5] [56].
However, it was only in 1942 that a connection was made between the virus and respiratory diseases. In 1980, it became apparent that distinct EHV types cause different diseases: EHV-1 is identified as equine abortion virus and EHV-4 as equine rhinopneumonitis virus [57] [58] [8].
Only in subsequent years were the remaining equine herpesviruses identified. In 1963, EHV-2 was initially isolated, yet it was not defined as the causative agent of keratoconjunctivitis for several years [5].
EHV-3 was isolated in Canada, Australia, and the United States of America (USA) in 1968 and was later confirmed as the causative agent of equine coital exanthema [59] [5].
EHV-5 is currently the Herpesvirus that we understood the least. It has been recently defined as the causative agent responsible for equine multinodular pulmonary fibrosis [60] [5].

2.2.2 Transmission

Latently infected horses are the principal reservoir of the EHV infection. The virus has a short environmental persistence, which is about 7 days with a maximum of 35 days of survival. The viruses are heat labile and can be inactivated by all main disinfectants [61] [62] [63] [64] [65].

The transmission of infection can be indirect by personnel and fomites, as well as direct from horse to horse. The most important and common route of transmission is via aerosol; in this

case aerosolized droplets of respiratory tract secretions are spread through the air and horses inhaling these get infected. The direct spread of the virus is also important, as respiratory tract secretions are spread on the surrounding environment of the infected horse, in water buckets, shared feeds or even via a nose-to-nose contact and can be inhaled or ingested by not infected horses [62] [66] [10].

As the virus can survive for some time in the environment an indirect contact is also possible. The infected horse spreads the virus onto everything it is in close contact with, such as grooming utilities, tack, and the clothes of personnel. Moreover, the virus is spread via the venereal route and a vertical transmission is also possible [62] [65] [66].

EHV-3, causing equine coital exanthema, is transmitted primarily through breeding of infected horses. The virus can also be transmitted trans-placentally to the fetus of infected mares, which mostly leads to abortion and to another potential source of infection due to infection of the aborted fetus, the placenta, and placental fluids [65] [67] [62].
The infection of foals can happen in their first months of life, even in the presence of antibodies, occasionally followed by respiratory signs [68].

2.2.3 Latency

One of the most important features of the EHV infection is its ability to persist in the host as a latent infection [38]. Almost every EHV can produce a latency in the host body (**Fig. 4.**). Latency refers to a persistent viral infection where the genome remains present, but the generation of infectious virions is limited due to restricted expression. In this stage the virus is invisible for the host's immune system [42] [38] [8] [69] [70] [71].

During a latent infection, the viral genome migrates to the nucleus of the host cell and forms an episome. The episome does not integrate into the host genome, leading to the transcription and translation of all genes being blocked, except for LATs (Latency Associated Transcripts). The target cells for EHV latency are Lymph nodes, PBL (peripheral blood lymphocytes) and trigeminal ganglia (**Fig.4)** [70] [50] [72][42].

The LAT Ribonucleic acid (RNA) prevents translation of the IE (Immediate Early) proteins by binding as an antisense RNA. The resulting double-stranded RNA is degraded by the cell [73] [74].

The reactivation of latency in the context of EHV infection is not yet fully comprehended, though it has been observed that a latent EHV infection can be reactivated by stress, transport, or even birth. During this reactivation phase, the characteristic symptoms of the disease may not always manifest, which in turn renders infected horses as unrecognized shedders contributing to the spread of the virus [75] [69].

Table 1: Classification of equid herpesviruses

Species	Sub family	Genus	Disease	Site of latent infection
EHV1	α	*Varicellovirus*	Rhino-pneumonitis, abortion, myelo-encephalopathy	Lymphoreticular system, circulating and lymph node CD8+ T cells, trigeminal ganglia
EHV2	γ	*Percavirus*	NA	Circulating lymphocytes and trigeminal ganglia
EHV3	α	*Varicellovirus*	Coital exanthema	Probably Sacral ganglia
EHV4	α	*Varicellovirus*	Rhino-pneumonitis	Lymphoreticular system, CD8+ circulating and lymph node T cells, trigeminal ganglia
EHV5	γ	*Percavirus*	NA	Circulating lymphocytes and trigeminal ganglia
EHV6	α	Unassigned	Coital exanthema	Not known
EHV7	γ	Unassigned	NA	Not known
EHV8	α	*Varicellovirus*	Rhinitis	Not known
EHV9	α	*Varicellovirus*	Gazelle and Equine neurological disease	Not known

α: Alphaherpesvirinae, γ: Gammaherpesvirinae, NA: Not applicable

Figure 4: Table of the EHV classification and site of latency [70].

2.3 Disease

2.3.1 Clinical signs

The clinical signs of an EHV infection depend on various points, such as the age of the horse, the virulence of the virus, the type and strain of virus as well as the overall condition of the infected horse [66] [38] [10].

EHV-1 and -4, cause various symptoms that are commonly diagnosed as the equine rhinopneumonitis, viral abortion, and EHM. Infected horses, that for instance, show signs such as a biphasic fever, nasal discharge, coughing, anorexia, lethargy, pharyngitis and enlarged lymph nodes are generally suspected to have equine rhinopneumonitis. Moreover,

these horses can show other symptoms such as an incoordination of the hindlimbs, ataxia, urine retention or dribbling up to a recumbency, confirming EHM [76] [77] [10].

In case of a viral abortion, mares can show general clinical signs of infection, such as fever, anorexia, lethargy, respiratory signs and enlarged lymph nodes, but the abort often happens without the patient producing more specific symptoms. This mainly occurs in late pregnancy but is also described in early pregnancy [65] [9] [77]

EHV-2 can lead to different clinical signs which vary between foals and adult horses, except for keratoconjunctivitis, as it can affect all age groups. It is characterized by a superficial lesion of the conjunctiva, epiphora, chemosis, hyperemia and blepharospasm. Young foals show signs of pharyngitis, lymphadenopathy, nasal discharge, cough fever and rhinitis, whilst adult horses show signs of lethargy, anorexia, and respiratory signs [15] [16].

The coital exanthema disease, caused by EHV-3 shows more specific clinical signs. It is starting with enlarged lymph nodes and the appearance of 1-2 millimeters (mm) reddened papules occurring on the penis and prepuce of stallions, as well as on the vagina, perineum and on teats of the mare. These papules can develop further to vesicles, pustules, erosions, ulcers and may become necrotic. Further, clinical signs including rectal sphincter fissures, a localized inflammation with reddening and edema of the genitals and vulval discharge may be seen [78] [79].

Characteristic clinical signs in horses that have been infected with EHV-5 correlated pulmonary nodular fibrosis are shown as an overall poor body condition and a slightly increased respiration rate, followed by increased breathing sounds, respiratory distress, sporadic coughing, and fever [80].

2.3.2 Diagnostic

A comprehensive clinical history and clinical examination are essential for an accurate evaluation, but do not provide a conclusive diagnosis of an EHV infection by themselves [65]. Therefore, laboratory diagnostic examination methods are required to detect the

causative agent and verify infection. Various diagnostic methods are utilized to identify the virus, these can be categorized into direct and indirect assay [65] [66] [10].
The direct methods include Polymerase Chain Reaction (PCR), Immunofluorescence (IF), Virus Isolation (VI), and histopathology, whereas the indirect methods consist of hematology, serology, Cerebrospinal Fluid (CSF) analysis, Complement Fixation Test (CFT) and Virus Neutralization (VN) [65] [66] [10].

For the detection of the virus, besides the possibility of detecting the virus by electron microscopy, it can be identified through isolation in a cell culture. To identify the viral antigens, the diagnostic methods of choice are the IF testing, as well as histopathology combined with Immunohistochemnistry (IHC). In addition, detection methods to identify the specific viral nucleic acids include in situ hybridization assay as well as different types of PCR (real-time , standard, insulated isothermal, and the allelic discrimination real-time PCR) [65] [66] [10].

For the indirect detection of EHV, the serological method of antibody detection includes CFT, Virus Neutralization Test (VNT), Enzyme-linked Immunosorbent Assay (ELISA) and Agar Gel Immunodiffusion Assay (AGID). Moreover, the analysis of hematology and CSF is also possible [81] [10] [81].

The Office International des Epizooties (OIE) recommends PCR for diagnosing EHV. The PCR technique is capable of detecting nucleotide sequences of EHV DNA. Various type-specific primers have been designed to discern between the different EHV viruses. Suitable specimens for PCR analysis include tissue samples from the aborted fetus, placental specimens, airway swabs or lavages, non-coagulated blood, and post-mortem samples of brain and spinal cord fluid [82] [66] [10] [65].

The ante-mortem diagnosis of latent infections is a major challenge. Reliable detection is usually not possible with the methods described above. The reasons for this are on the one hand that latently infected horses show no signs of infection, and on the other hand that the virus is in an inactive state so that it is not recognized by the immune system [70].

In vitro co-cultivation of lymphocytes provides a clear result and is mentioned as the gold standard, however a negative result doesn’t implicit an absence of latent infection. Another

possibility to detect a latent infection can be provided by performing a real-time (RT) -PCR, to detect the presence of LATs which are the only genes getting transcribed during latency. Furthermore, the detection of VN antibody titers can indicate a latent infection as well as performing a PCR for the detection of late gB genes in DNA, while they are absent in RNA [70] [81].

2.3.3 Treatment

Treating an EHV infection involves assessing various factors and therefore often requires a sophisticated approach. Firstly, veterinarians need to establish which strain of EHV is causing the illness, as well as the associated clinical symptoms. Secondly, the severity of the condition must be considered. While veterinarians ultimately determine treatment, research provides insight into the effectiveness of different drugs in combating the infection [66] [63] [10].

In the event of a respiratory disease, it is necessary to isolate both the diseased horses and those that have been in contact with it. Additionally, to prevent infection in other horses, it is important to establish a quarantine-like environment with proper hygienic measures. As this respiratory illness usually appears as self-limiting and mild, no special treatment is necessary. However, it is crucial to refrain from exercising horses for a week after detecting clinical signs, as it may prompt reactivation of latency [8] [10] [62] [66].

To decrease the clinical signs of a viral infection, it's possible to treat the horse with non-steroidal anti-inflammatory drugs (NSAID's) and antipyretics and to prevent a secondary infection, the usage of antibiotics is recommended [65] [83].

In instances of equine multinodular pulmonary fibrosis (EMPF), research has demonstrated enhanced recovery through the implementation of fluid therapy, specifically using ringer's lactate, as well as dexamethasone, doxycycline, and valacyclovir [80]. However, since it is a chronic condition, a cure is not achievable. Another therapeutic method is administering corticosteroids and antibiotics, such as cefquinome and prednisolone [84].

If EHM develops, strict quarantine must be implemented immediately, followed by appropriate supportive care, including adequate hydration and nutrition, as well as a rectal examination. If necessary, retained feces and urine should be removed by catheterization. The medical treatment involves using NSAIDs in the form of meloxicam to reduce central

nervous system (CNS) inflammation and a prophylactic treatment with trimethoprim-sulfamethoxazole in the case of catheterization. The administration of dexamethasone is added if neurological symptoms appear [63] [54].

Treatment for ECE is non-specific. Sexual abstinence is primarily enforced to allow successful healing of genital lesions and to contain the virus spread. Supportive broad-spectrum antibiotics are administered to prevent secondary infections. Additionally, trials have investigated the effectiveness of Acyclovir (ACV) and Ganciclovir (GCV) in reducing viral activity. In addition, separating infected horses is essential, along with implementing general hygiene measures [79] [85]

2.4 Prevention and control

2.4.1 Epidemiological measures

Both equine herpesviruses 1 and 4 (EHV-1 and -4) are worldwide equine pathogens causing respiratory disease (EHV-1, EHV-4), abortion and myeloencephalopathy (EHV-1) [86]. Under conditions of stress, competing, infections and immune suppression, the pathogen can be reactivated and shed unnoticed [87][88]. In recent years, there have been several reports of nosocomial outbreaks of EHV-1 in hospitalized horses, some of which resulted in EHM. Due to the high level of contagiousness, horses actively shedding EHV-1 should not share 'common airspace' with other horses and should be kept under strict control [89].

Preventing the virus spread through the herd is essential. It is important to demarcate stable units, restrict movement and crossing of horses, and keep activity to a minimum. Furthermore, avoid unnecessary movement of people between units and use stable staff strategically (separate teams, work from clean to dirty). The strategic placement of shoe disinfection mats between stalls is necessary [66] [9].
If horses are kept in individual stalls, an individual gown and disposable gloves must be provided for each horse. The gown is best hung at the entrance to the stall. A new pair of gloves must be worn each time contact is made with the horse. Contact with the horse's head and nostrils (the largest source of excrement) should be kept to a minimum [90].

After leaving the stable, shoes should be walked directly over a disinfectant mat or into a disinfectant bath. To wash hands between each contact with the horse is also indispensable. In the neurological form of the disease, EHV-1 associated abortions may occur at the same time. Placenta, amniotic fluid, amniotic sac, and aborted foal contain large amounts of infectious virus. Mares continue to shed virus with the lochia for up to five days after abortion. If it is possible to isolate a feverish horse, this should be done immediately. When moving horses, ensure that other horses do not meet the feverish horse. If direct contact (nose to nose) between neighboring horses is possible through a permeable partition between two stalls, this should be covered with plastic sheeting [90].

As far as vaccinations are concerned, the pressure of infection is reduced optimally when all animals inhabiting a stable are vaccinated. Especially when moving horses between stables, or before races, a basic vaccination should be administered. Subsequently a 14-day rest period is necessary for the development of immunity and should therefore be observed.
A prerequisite for the development and maintenance of immunity against infections caused by herpesviruses is the regular vaccination of all animals in the breeding stock in accordance with the prescribed vaccination dates. For all unvaccinated horses intended for breeding, it is recommended that basic vaccination be carried out in quarantine and that the 14-day rest period necessary for the development of immunity be observed. Sick horses showing symptoms of respiratory disease should be isolated from healthy horses [91].
For the prevention of ECE, considering that the main negative consequence is the occurrence of the disease in stallions during the breeding season, preventive measures are mainly based on clinical examination of mares before mating to screen out those with clinical signs of ECE. However, this method does not identify subclinical infected animals [79].

Management following an outbreak includes the lifting of quarantine. This is done when the normal elimination period for EHV-1 in adult horses has elapsed three times, i.e., three times seven days, for a total of 21 days. A final disinfection of the premises must also be carried out. Rapid decontamination of surfaces in premises where an EHV-1 epidemic has occurred can be achieved by thorough cleaning with detergents and water, followed by chemical disinfection with compounds containing phenol or iodine. Items to be cleaned and disinfected include stable and corridor surfaces, used bedding, bridles, lead ropes, feed and water containers, staff boots and outer clothing, instruments of treatment, grooming, cleaning, and mucking out equipment and the interior of horse transport vehicles [92] [93].

2.4.2 Vaccine

Vaccinations help to maintain and promote the health and performance of horses. They protect the individual animal and the horse population [94].

To date, there is no vaccination available for EHV types 2, 3 and 5 [79] [95]. Vaccination against EHV-1 and EHV-4 is a preventative measure to manage EHV infection.
Live attenuated and inactivated vaccines have been developed for use in horses. Clinical studies indicate that vaccination against EHV-1 and -4 can decrease clinical signs of respiratory symptoms and abortions. Nevertheless, there is currently no vaccine available that fully protects against neurological disease [10] [65].

The vaccinations are administered following a predetermined schedule, set by the vaccine developer. There are several licensed inactivated vaccines on the market, as well as a live vaccine [96].

BioEquin H is an inactivated vaccine from Bioveta, licensed since 2017. It is presented as an emulsion for injection and is used for the active immunization of horses to prevent respiratory infections and clinical signs caused by EHV-1. It has also been shown to reduce abortion in mares caused by EHV-1. The active ingredient is an inactivated EHV-1 with a minimum 2,1 $\log_{10}$ virus neutralization index.
The vaccination schedule for basic immunization recommends two single injections. The first vaccination is given at six months of age, followed by a second injection four weeks later. Subsequent boosters are given at three months and then every six months. Pregnant mares are vaccinated in the second month after conception, in the fifth or sixth month and in the ninth month of pregnancy [97] [98].

Another inactivated vaccine is Equip® EHV-1, -4, produced by Zoetis. This is a combined vaccine containing equine herpesvirus types 1 and 4 for injection into horses older than three months of age [99].

The active ingredients are:

- equine herpesvirus type 1, strain 438/77, inactivated relative potency (RP) > 1 with the rabbit kidney (RK) -13 cell line host system.

– equine herpesvirus type 4, strain 405/76, inactivated RP > 1 with the Biologics Standards-Cercopithecus-1 (BSC-1) cell line host system.

It is intended for active immunization of healthy horses against respiratory diseases caused by EHV-1 and/or EHV-4 and for use in healthy, immunocompetent mares as a measure to prevent abortion due to EHV infection. The duration of immunity after primary immunization is six months [99].

The vaccination program against respiratory diseases includes a basic immunization consisting of two vaccinations. The first vaccination is given at five to six months of age, the second four to six weeks later. In cases of high infection pressure and insufficient maternal antibody titers, an additional vaccination can be given from the third month. Repeat vaccinations are then given every six months. To prevent abortion, pregnant mares are vaccinated with one dose each in the fifth, seventh and ninth months of pregnancy [99].

EquiShield EHV, an injectable emulsion for horses, is another inactivated vaccine. It is indicated for active immunization of horses to reduce clinical signs and virus shedding in respiratory infections, caused by EHV-1. Onset of immunity is two weeks after administration of the second vaccine dose. Duration of immunity is six months after administration of the third vaccine dose and durable immunity has only been demonstrated after three vaccinations [91].

It can also be used for active immunization of pregnant mares to reduce the incidence of abortion due to EHV-1 infection. Onset of immunity is three weeks after administration of the third dose during pregnancy and duration of immunity is until the end of pregnancy [91] The active ingredient is an inactivated EHV-1 (Bio 82: EHV-1) with a minimum 2 $\log_{10}$ VNI [91].

The vaccination schedule is as follows:

– the basic immunization consists of three single doses, the first dose being given at six months of age, the second four weeks later and the third three months after the second dose.
– The single-dose booster vaccination is given six months after completion of the primary vaccination, and further boosters are given every six months.

- When vaccinating pregnant mares, one dose of vaccine is given in the second month after conception and then in the fifth or sixth and ninth months of pregnancy. This three-dose schedule should be repeated for subsequent pregnancies [91].

The only live vaccine against EHV is Prevaccinol® preproduced by Merck Sharp & Dohme (MSD). It contains, lyophilizate and solvent for the preparation of an injection suspension for horses and ponies [100].

Immunologically active ingredients are:

- EHV-1, strain RAC-H, live, attenuated, min. 10^6, max. $10^{7.7}$ tissue culture infectious dose 50% ($TCID_{50}$), with the host system of porcine kidney cell culture.
- the solvent contains phosphate buffer [100].

It is applied to actively immunize horses and ponies and to thereby reduce EHV-1 infections and clinical signs of respiratory disease caused by the virus. When used as recommended, the vaccine induces CF and VN antibodies that significantly reduce viremia frequency, duration and level of virus shedding, body temperature elevations and clinical signs of rhinopneumonitis as demonstrated in a challenge study with a pathogenic strain of EHV-1. Onset of immunity is two to four weeks after primary immunization with a duration of immunity of six months [100].

The basic immunization consists of two injections of one dose (5 milliliters) each, given at intervals of three to four months, starting at the earliest at six months of age. Boosters are given every six months [100].

3 EHV-1 outbreak 2021

3.1 EHV-1 outbreak in Valencia, Spain

3.1.1 General data

In the spring of 2021, a massive outbreak of the neurological form of EHV-1 occurred at the CES Valencia Tour international horse show in Valencia, Spain. Due to the rapid spread of the virus, the outbreak quickly spread beyond Spain, resulting in a widespread EHV-1 outbreak [101] [102].

Other international competitions were quickly affected, as well as the home farms of the competition riders. A total of ten countries were confirmed to be affected of this outbreak. These include Belgium, Denmark, France, Germany, Italy, Qatar, Spain, Slovakia, Sweden, and Switzerland [103].

The CES Valencia Tour is located on a large site, see **Fig. 5** below. There are three outdoor riding arenas (A1, A2, A3), an indoor riding arena (A4), a training arena (A5), two lunging arenas (A6, A7), an eight-horse walker (A8) and several paddocks (A9). For the accommodation of the horses, the site offers a permanent stable with 80 boxes (E2) and several stable tents with 440 tent boxes [104] [103].

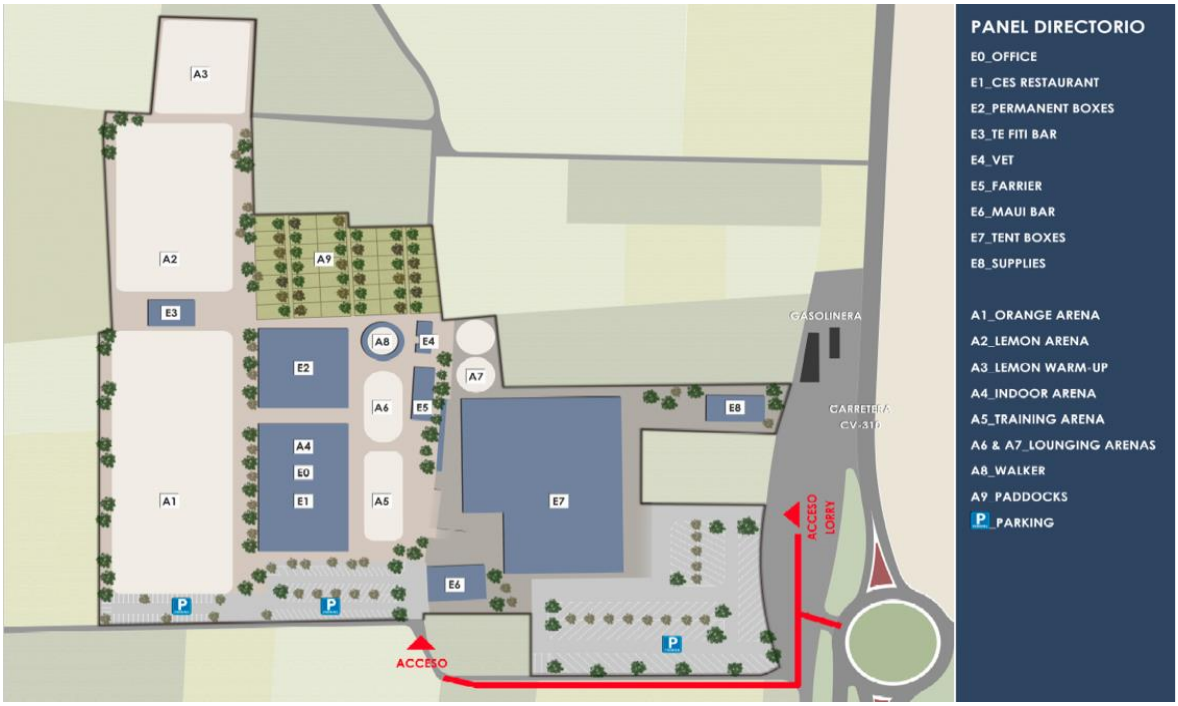

Figure 5: Facilities of the CES Valencia Tour [104].

Over the course of four weeks, 752 horses participated in the CES Valencia Tour. To contain further spread, the Deutsche Reiterliche Vereinigung (FN) suspended national competition sport in Germany for four weeks. The Fédération Équestre Internationale (FEI) suspended the international equestrian season in Central Europe for eight weeks. In addition, the federations banned horses that had taken part in the affected events from competing. They were only allowed to compete again once quarantine and testing requirements had been met. By March 26th, 2021, a total of 18 horses had died in the outbreak. Eleven were recorded in Spain, five in Germany and two in Belgium [105] [106] [107] [103].

3.1.2 Management of the outbreak

The FEI Veterinary Department was informed on February 20th, 2021, about horses on the CES Valencia Spring Tour grounds suffering from pyrexia. Furthermore, a horse suffering from EHV-1 was reported, which also took part in the event but had already returned to France.

As EHV-1 is a disease controlled and notifiable by the authorities in Spain, the show was cancelled, and the facility was closed on February 22nd [103] [102] [104].

Most of the participants went home, but 160 horses remained on the CES area. Of these horses on site, diagnostic, clinical and epidemiological data were collected [102] [104].

Of these horses, 118 were found to be clinically or sub-clinically ill and eight had to be euthanized. In addition, the FEI has received further reports of confirmed cases of EHV-1 in horses that participated in the event. As a result, the FEI has ordered the cancellation of all shows in mainland Europe between March 1st and April 11th to prevent further transmission of the disease [102] [107].

The situation on the ground in Valencia was slowly improving. A total of 83 horses showed clinical signs and were treated, but none of these horses were recumbent and required a sling for support. Fifteen horses were treated in external clinics, thirteen in Valencia and two in Barcelona.

The French Federation has organized special stabling in France for horses travelling through the country where they can be housed under the required biosecurity conditions with disinfection procedures and on-site veterinary care [103].

A biosecurity protocol for the return of French horses was drawn up by the French authorities and submitted to the Spanish government. This protocol stipulated that three negative PCR tests at an interval of three weeks were required to end the quarantine period and thus release the horses for return to France. This was based on a thorough clinical examination excluding clinical signs such as coughing, ataxia and pyrexia. This repatriation was possible from the March 11th. However, the horses were isolated in France, at a French Equestrian Federation facility in Lamotte-Beuvron [104].

3.1.3 Diagnostic and clinical signs

The horses present on the premises showed classic clinical signs of EHV-1 disease. However, a distinction must be made between severe and mild disease and even asymptomatic disease [104].

The clinical signs of the severely affected horses ranged from the onset of pyrexia and coughing to severe neurological signs and even recumbency. The mild cases showed only pyrexia and coughing [104] [107].

Nasal swabs and blood samples were taken for laboratory diagnosis. PCR and VN confirmed or excluded EHV-1 disease.

A study was carried out on the detection of EHV-1 in urine samples during outbreaks of EHM. To date, there have been no reports on the excretion of EHV-1 in urine and the possibility of detecting the virus in urine samples. In the study, real-time PCR was performed on buffy coat (BC), nasal swab (NS) and urine samples. The result confirmed eleven out of 18 positive urine samples [76].

3.1.4 Genome Sequences

Two studies on the Valencia events investigated the gene sequences of the active EHV-1 outbreak. Firstly, an eleven-year-old gelding was examined in Switzerland who had previously been in the CES in Valencia. Clinically, he showed pyrexia but no neurological signs. A nasal swab was taken on February 25th,2021, for further clarification [101].

On the other hand, several horses were examined in Belgium and France, which also attended the Valencia CES. Here, blood samples and nasal swabs were used for the investigation [106].

As a result, six genome sequences could be detected. Of these six, five were recorded in France and Belgium and one was recorded in Switzerland (**Fig. 6**).

These are:

- Equid alphaherpesvirus 1 strain H3_Allg_92_21/CH/2021, partial genome
- Equid alphaherpesvirus 1 strain BE/21P40/2021, partial genome
- Equid alphaherpesvirus 1 strain BE/21P41/2021, partial genome
- Equid alphaherpesvirus 1 strain BE/21P43_BD5/2021, partial genome
- Equid alphaherpesvirus 1 strain FR/Valencia1/2021, partial genome
- Equid alphaherpesvirus 1 strain FR/Valencia2/2021, partial genome [101] [106].

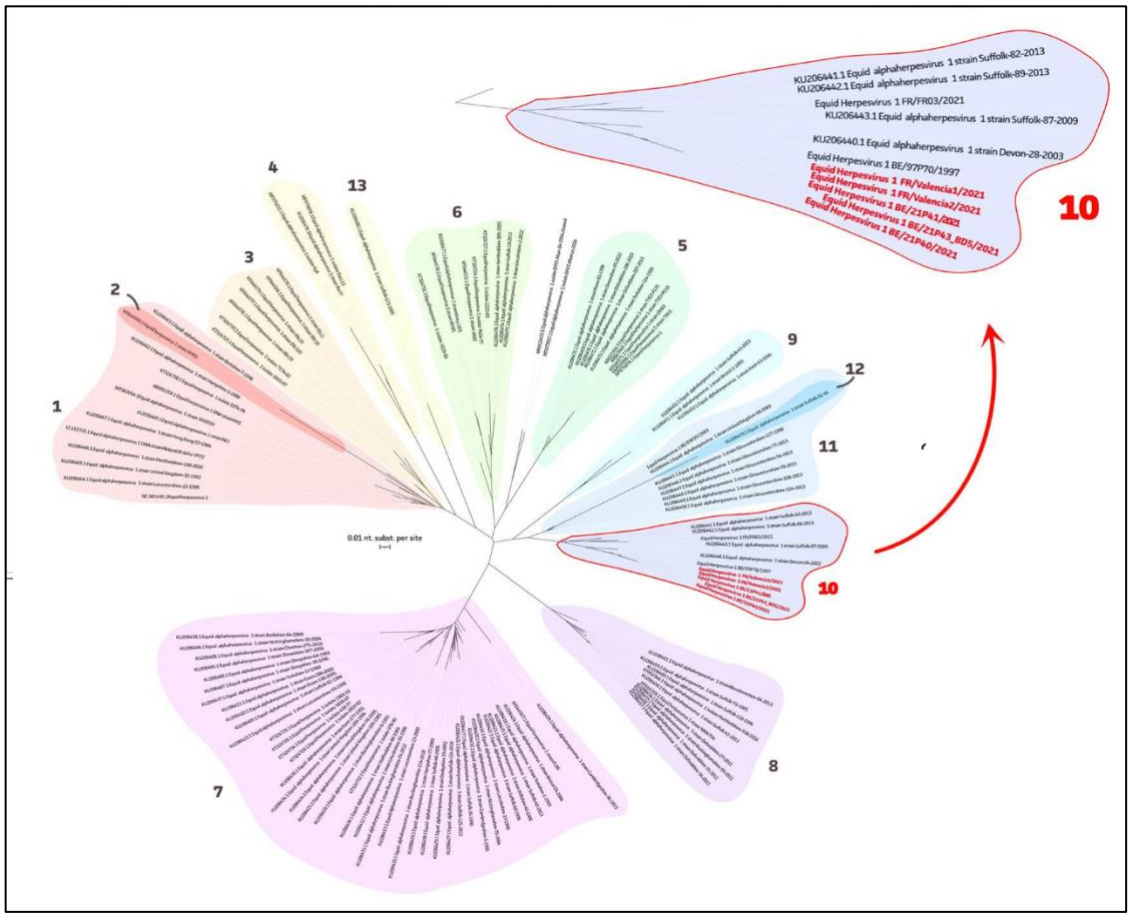

Figure 6: Phylogenetic classification of the new EHV-1 sequences determined from the 2021 outbreak (three from Belgium, two from France) along with all previously available sequences [101].

3.1.5 Epidemiological situation in affected countries

The situation in Germany was as follows.
EHV-1 is not notifiable or reportable in Germany, so there is no accurate overview of the outbreaks, nor are there any legal requirements for the horses returning from Spain. The FN has called on the riders concerned to exercise extra caution and has informed them of the necessary hygiene measures [108] .

However, it is known that the horses of riders of German nationality who returned home from Valencia, was taken well care of in their home stables or in clinics, separated from other horses. Some showed symptoms of varying severity, others have been tested negative and showed no signs of illness. The riders did everything they could do to prevent the virus from spreading in their home stables or beyond. To this point, the positive cases linked to Valencia are confined to the stables of the Valencia returnees [102] [103].

The situation in Doha, after the initial outbreak in Valencia, was not very severe. A total of four horses travelled from CES to Qatar. Two tested positive for EHV-1. Neither of the horses showed any symptoms of EHV-1 infection. Both horses were well treated in the local clinic, separated from other horses.
However, after the horses returned to Europe, one horse spread EHV-1 in the home barn, resulting in three other infected horses with a severe course of EHM leading to euthanasia. Neonatal deaths and abortions were also reported [102] [103].

The FEI was not aware of any further positive tests in Doha and supported the continuation of the show in Doha, as the riders and horses have already been there for almost two weeks. They were closely monitored, and the necessary hygiene measures were easily implemented and adhered to at the facility [103] [102] [108].

The organizers of the Sunshine Tour in Vejer de la Frontera, Spain, have announced that a horse there showed neurological symptoms like EHV-1 on the morning March 4th, but had already been isolated two kilometers from the show venue on February 26th. The horse had been brought to Vejer from its home stable in Belgium and was initially asymptomatic and healthy [103] [102] [108].

On the morning February 26th, a vet noticed that the horse had fever, and it was immediately isolated. An EHV-1 Test was Negative. In consultation with the FEI and local authorities, the organizers decided on the march 4th to close the show early on March 7th. However, following a comprehensive risk assessment, it was also decided to continue the show until then to ensure an orderly departure of the horses [108] [103].

On March 6th, the FEI has been informed that a second horse has been isolated at the Spanish Sunshine Tour venue in Vejer de la Frontera after developing mild neurological signs and a slightly elevated temperature. As this was the second horse showing symptoms of EHV-1 in Vejer, the FEI has informed the organizer that the Sunshine Tour will be cancelled with immediate effect, one day earlier than previous decided [108] [103].

Both horses were in the isolation stables two kilometers from the venue. To ensure an orderly and safe departure of the healthy horses remaining at the venue, the competent Spanish authority was on site and issued the necessary health certificates for the horses to leave [108] [103].

3.2 Regulation of the Fédération Équestre Internationale

As a result of the serious EHV-1 outbreak in Valencia, the FEI has issued international regulations to prevent this from happening in the future.

3.2.1 Biosecurity Protocol

A general biosecurity guide has been published. This provides sound information and officially tested practices for the management of EHV-1 outbreaks to improve the containment and spread of the disease.
The first point in the guide describes how to set up an isolation unit, covering important aspects such as the choice of the best place to isolate the sick horses and the materials used in the stables regarding disinfection. Secondly, the access to isolation is explained. This section states, to allow access to only a few people who care for the horses, to create clear

boundaries to prevent inadvertent trespassing and there should also be sufficient distance from the other horses who might need to pass by the Isolation. Where possible, groups of horses travelling together should also be housed together, but not directly stall to stall. General hygiene measures should be observed, and communal troughs should not be used. Each horse that has been isolated should be dated.
Monitoring of the horses is also described in terms of monitoring the health of the horses, feed and water, staff, equipment, and other animals. The last point provides information on leaving isolation with a special note on thorough disinfection [109].

3.2.2 Long-term regulations

Critical measures and requirements for a safe return to competition in continental Europe following the EHV-1 outbreak have been adopted and came into force on April 12th, 2021. These include the protection of FEI horses and global equestrian sport from the consequences of infectious diseases before, during and after FEI events. To ensure the good health status of sport horses to global, continental, and national veterinary authorities and organizations in order of maintaining and further improve the conditions for the international transport of these horses [110].
Mandatory FEI Veterinary Regulations includes in total 16 listed measures, divided into the preparations of the venue before the event starts, pre-event preparations, examination of the horses on arrival and onsite actions should the necessity arise [110].

Pre-event preparation of the venue includes the following measures:

- A biosecurity plan for the event is mandatory, including an emergency plan in the event of an infectious disease outbreak.
- A map showing the location of each competitor's horse must be drawn up before the horses arrive and updated if there are any changes.
- Stables must be disinfected in accordance with Article 1017 of the FEI Rules.
- Washbasins are required at entrances and exits and hand disinfection is required in the stables.
- Isolated stalls should not be in the normal stalls or in the same air space as non-isolated horses. It must be at least 50 meters away from any flow of horses.

- The team working in isolation must not enter the normal stables without first being completely cleaned and disinfected.
- Unauthorized access to the stables and other animals is prohibited.
- The isolation unit must have at least two individual stalls for every 100 horses.
- If the clinic or treatment stables are used on site, a cleaning and disinfection protocol must be documented.
- Regarding water and washing facilities, it is important not to use common troughs, wash basins must be clearly marked, and it is mandatory to wash and disinfect hands before entering and leaving the stables [110].

The list of checks on arrival includes.

- The normal procedure of checking for signs of infectious disease and checking for equine influenza vaccination.
- Horses with an elevated temperature (above 38.5°C) are subject to a specific protocol. Owners will be required to take the horse's temperature in the three days prior to arrival and record it on the FEI app [110].
- At the show venue the measures conclude:
- The temperature of the horses must be taken twice a day and recorded on a clipboard outside the stable.
- Measures will also be taken in relation to staff. Access to the stables will be restricted. Access will only be granted to essential staff [110].

4 Conclusion

In summary, this thesis has explored the complicated and multi-faceted landscape of EHV, with a particular focus on the 2021 outbreak in Valencia, Spain. Through an in-depth examination of EHV virology, pathogenesis, clinical manifestations, transmission dynamics and control measures, we have gained a comprehensive understanding of the challenges these pathogens pose to the equine industry and the sport of riding. The Valencia outbreak, which has been the main motivation for this thesis, has provided us with important experiences and insights, that have far-reaching implications for the health and welfare of horses and the equine industry.

It has shed light onto the requirements needed for dealing with infectious diseases in competitive riding and should therefore spark more discussions about health and safety measures at such events. Especially when it comes to prevention.

One of the key lessons learned from this research is the importance of preparedness and contingency planning in the equine industry. The Valencia outbreak demonstrated the vulnerability of equine populations to such viral threats and the importance of a timely and coordinated response. Improved surveillance, early detection and communication between stakeholders are important components of a comprehensive strategy to mitigate the consequences of future virus outbreaks.

In addition, the lack of literature surrounding such infectious disease outbreaks in the competitive riding industry highlights the need for continued research. Including, the development of new therapeutics and vaccines, to improve the prevention and control of these infections. Equally important is the dissemination of knowledge and best practices among horse owners, veterinarians, and industry professionals to promote proactive measures and improved biosecurity protocols.

The Valencia outbreak in 2021 also highlighted the global and interconnected nature of the equine world, as EHV spread rapidly through international horse transport and equestrian events. The rapid spread of the virus and the significant impact on equine health and equestrian sport highlight the urgent need for enhanced biosecurity measures, robust diagnostic capabilities, and effective vaccination strategies. The ability of EHV to manifest itself in a variety of clinical forms, from respiratory symptoms to abortion and neurological disorders, underlines the complexity of managing and preventing these infections.

In conclusion, the described event was a stark reminder of the challenges posed by EHV and the critical role that research, preparedness and collaboration play in protecting the health of horses and the sustainability of the equine industry. By learning the lessons of Valencia and building on the knowledge gained from this work, we can work together to better protect the equine population from the threats posed by equine herpesviruses and ensure a healthier and more resilient future for these great animals.

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6 Figures

7 Acknowledgement

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8 Documents

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Thesis progress report for veterinary students

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Department:	Department of Microbiology and Infectious Diseases
Thesis title:	**An overview of Equine Herpesvirus-1 with special regard to the 2021 spring outbreak in Europe**

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	02	08	Defining topic details	
2.	2023	03	21	Finalizing concept for thesis structure	
3.	2023	04	17	Collecting key literature	
4.	2023	04	19	Reviewing selected papers	
5.	2023	06	05	Discussing tasks for summer	

Grade achieved at the end of the first semester: 5

1

Consultation – 2nd semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	08	22	Checking early draft	
2.	2023	08	25	Checking plan of chapters	
3.	2023	09	07	Checking draft progress	
4.	2023	10	18	Corrections of final draft	
5.	2023	11	02	Finalizing thesis, additional paperwork	

Grade achieved at the end of the second semester: ……5……..

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

……..
signature of the supervisor

Signature of the student: ……

Signature of the secretary of the department: Bakainé M. Mária

Date of handing the thesis in 06.11.2023.

2

I hereby confirm that I am familiar with the content of the thesis entitled

AN OVERVIEW OF EQUINE HERPESVIRUSES WITH SPECIAL

REGARD TO THE 2021 SPRING EHV-1 OUTBREAK IN EUROPE

..... written by MARYSE JOËLLE FREIBURGHAUS .....

(student name) which I deem suitable for submission and defence.

Date: Budapest, 03 day 11 month 2023 year

DR. MAROSI ANDRÁS

..... Supervisor name and signature

DEP. OF MICROBIOLOGY

AND INFECTIOUS DISEASES

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