EHV 1&4

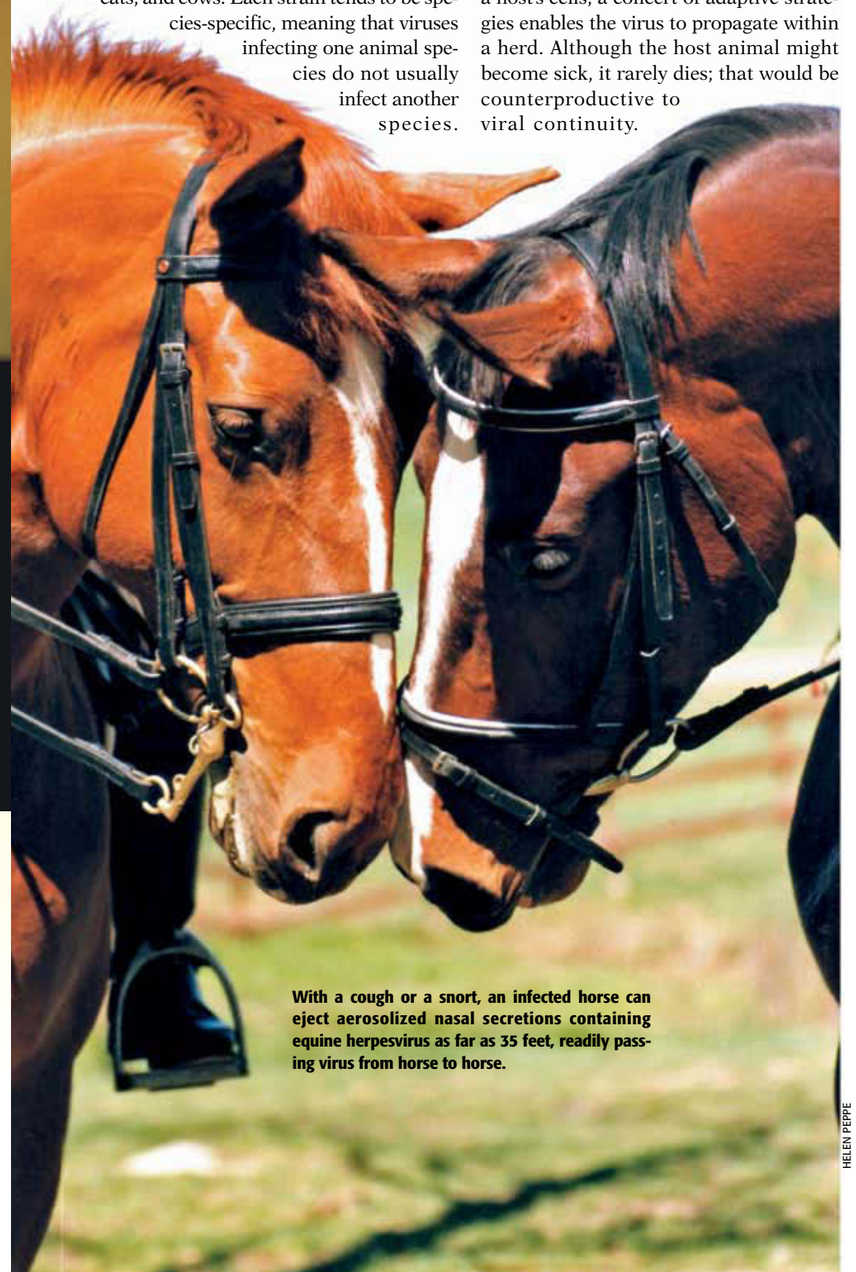
BY NANCY S. LOVING, DVM

Herpesvirus is a particularly well-evolved virus that occurs in many mammals, such as humans, horses, cats, and cows. Each strain tends to be species-specific, meaning that viruses infecting one animal species do not usually infect another species.

In the world of microbes, viruses are specialized in their ability to infect and survive within a host. After a virus inserts itself into a host's cells, a concert of adaptive strategies enables the virus to propagate within a herd. Although the host animal might become sick, it rarely dies; that would be counterproductive to viral continuity. Instead, an infected animal serves as a reservoir for viral infection.

Viruses are masters at the game of hide-and-seek. Some, like influenza virus, mutate to elude recognition by a host's immune response. Others, like equine infectious anemia, debilitate a host's immune system so it cannot counteract the virus.

Herpesvirus has developed its own adaptation: It maintains itself within its host by evading detection by the host's immune system. And herpesvirus is unique in its ability to persist in the host in a latent form, recurring at intermittent periods that correspond with stress events.



With a cough or a snort, an infected horse can eject aerosolized nasal secretions containing equine herpesvirus as far as 35 feet, readily passing virus from horse to horse.

HELEN PEPPE

Respiratory disease, abortion, and neurologic disease are all caused by herpesviruses

In humans, we are most familiar with herpesvirus in the form of recurrent cold sores. In the horse, equine herpesvirus (EHV) is classified into five different strains: EHV-1, EHV-2, EHV-3, EHV-4, and EHV-5. Of these, EHV-1 and EHV-4 are the strains associated with viral respiratory disease. EHV-1 is the most prevalent concern in horse populations not only because its respiratory disease is more virulent than that caused by EHV-4, but also because it is incriminated in causing viral abortion or neurologic disease (myeloencephalopathy).

Spread of Infection

With a cough or a snort, an infected horse can eject aerosolized nasal secretions containing equine herpesvirus as

Editor's Note

This is the sixth in a 12-part series of articles on vaccinations for horses.

PART 6

far as 35 feet, readily passing virus from horse to horse. Yet this virus is best transmitted through direct contact rather than aerosol transmission. Direct nose-to-nose contact passes copious quantities of viral material from one horse to another, as do shared water sources that are contaminated with nasal secretions. Infected organic material clings to feed, water tanks, stalls, horse trailers, tack, equipment, wheelbarrows, rakes, muck buckets, shoes, and clothing with the potential to move across a farm. Direct contact with an aborted fetus or placental tissue readily spreads infection due to the high concentration of virus within aborted tissues.

Of key importance in transmission of this virus is exposure by carrier horses that are incubating disease and not yet showing clinical signs, or from horses that silently shed virus when a latent infection is reactivated by stress or illness.

Latent Infection

What makes herpesvirus peculiarly unique is its ability to persist in a latent state, reappearing at intervals through an animal's life. Herpesvirus might be present in as many as 50% of adult horses, maintaining its presence in its hideout place within the trigeminal nerve of the face or within specialized white blood cells of the lymphatic system. It is clever in its ability to evade a host's immune recognition. While virus rests in a dormant state within latently infected cells, it does not turn on its machinery to replicate itself. Instead, it lurks and waits. During this stealth period while it is not expressing antigenic proteins that might alert the host to its presence, it is "silent" to the immune system, effectively escaping detection and destruction by the horse.

During stressful periods associated with training, competition, transport, management changes, or illness, high levels of circulating corticosteroids suppress a host's normal defense mechanisms. Poor nutrition, a heavy parasite load, overcrowding, and rigorous climatic events are other stressors that adversely affect a horse's immune defenses. It is during stress periods that latent virus is reactivated and shed into the nasal secretions. A horse might appear clinically normal, yet he serves as a silent shedder. This increases the potential to spread virus within a herd to individuals whose immune systems have not been previously challenged by herpesvirus.

George Allen, PhD, of the University of Kentucky's Gluck Equine Research Center, is an authority on equine herpesvirus. He suggests that transmission maintains itself within a horse population in several ways:

- Passage from a latently infected mare to her foal;
- Persistence of infection in a latently infected youngster into adult life; and
- Reactivation of latent virus to pass from horse to horse of any age.

Invasion of the Host

To understand the dynamics of effective vaccine control, it is helpful to understand how herpesvirus infects a horse. Its primary attack assaults the respiratory tract within 48 hours of exposure. Virus entering there attempts to attach to and penetrate epithelial cells lining the airways. At that site in the respiratory lining, a horse's immune response has its first opportunity to neutralize the virus. It can do this through protective antibodies that prevent cellular invasion, and by rallying specialized white blood cells contained within the clearance apparatus (mucociliary system) of the respiratory tract. It is there a viral vaccine has the best effect by priming the system to induce antibodies, which recognize specific foreign proteins on herpesvirus particles before they invade the host's cells.


DUSTY PERIN

Direct nose-to-nose contact passes copious quantities of viral material from one horse to another, as do shared water sources that are contaminated with nasal secretions.

To mount an effective immune response, it is important for the respiratory lining to remain healthy and in optimal working condition. Poor air quality, dust, allergic airway disease, and other viruses create conditions that detract mightily from a host's defensive immune function in the upper airways.

If herpesvirus breaches the defenses of the upper respiratory tract, it then follows two routes: In 48 hours it makes its way to the trigeminal nerve of the face, where it will remain as a latent infection as described previously. The other route is dissemination within 72 hours to the lymphatic and blood circulatory systems. Once virus infects a white blood cell, it is able to circulate through the bloodstream without interference from the host immune system even in the presence of high antibody titers.

Researching herpesvirus immunity is the special focus of Cormac Breathnach, PhD, who earned his doctorate under the mentorship of Allen at the Gluck Center. Breathnach observes, "The virus evades the host antibody response by remaining intracellular (within a host cell) at virtually all stages of its movement throughout the body. This is a critical strategy by which it circumvents anti-EHV antibodies, which are the primary response induced by most vaccines."

Effective immune defense then relies on cell-mediated mechanisms whereby white blood cells engulf virus-infected cells. During the phase when virus is circulating throughout the body (viremia), herpesvirus further interferes with normal defensive response mechanisms of cytotoxic T-lymphocytes that are meant to eliminate virus-infected cells.

The viremic phase lasts from seven to 21 days, and during that time virus-infected cells can spread to other organs, such as a pregnant uterus and fetus to cause abortion, the central nervous system to elicit myeloencephalitis, or the eye to induce ocular disease like chorioretinitis. Typically, a horse that develops viral abortion or viral neurologic disease will have mild respiratory disease and/or fever in the two weeks preceding clinical evidence of reproductive or neurologic disease, albeit the signs might be so subtle as to be unnoticed.


COURTESY DR. DAVID POWELL

Direct contact with aborted fetus or placental tissue readily spreads infection due to the high concentration of virus within aborted tissues.

Clinical Signs

Although equine herpesvirus is most prevalent in horses younger than two years of age, it can infect horses of any age. Initially, infection with herpesvirus produces mild respiratory signs of watery nasal discharge, mild fever, and cough. There might be pinpoint hemorrhages (petechiations) on the mucous membranes. Some horses also develop edema (fluid swelling) of the limbs or abdomen. After several days, the clear nasal discharge turns progressively thicker, leaving a crust around the nostrils. Less than a week into the illness, this turns into an obvious yellowish, snotty discharge due to bacterial invasion of damaged cells lining the respiratory tract.

Once the infection moves to the lymph nodes in those first few days, it can reach a pregnant uterus or the central nervous system through blood circulation. Direct damage to the lining of the blood vessels adversely affects these organs. Abortion results from malnourishment of the fetus related to blood vessel damage within the uterus.

Breathnach explains the process leading to abortion: "Farm owners and breeders often note that mares appeared 'perfectly normal' prior to aborting virus-positive fetuses. One of two things can have happened. Either the infecting virus successfully reached the draining lymph nodes despite only causing an inapparent subclinical infection and established sufficient viremia for abortion (or neurologic disease) to occur, or the mare was latently infected with the virus, which became reactivated through stress, and the abortive infection 'occurred from within.'


PAULA DA SILVA

The recommended protocol for protecting pregnant mares against viral abortion is to administer herpesvirus vaccine prior to breeding, then at five, seven, and nine months of gestation.

"Reactivated virus emerging from lymphocytes or from the central nervous system can establish viremia in the absence of clinical disease in the upper respiratory tract," he continues. "Once viremia is established, all bets are off. This is one of the important features of EHV-1 that makes it so difficult to control. A mare that never showed a fever or runny nose can abort an EHV-1-laden fetus, and this can lead to an abortion storm."

A mare infected with equine herpesvirus might abort in the latter months of gestation, or an infected foal might be stillborn or born very weak and unlikely to survive due to viral pneumonia.

Allen comments, "For the last 25 years (following the commencement of widespread vaccination in 1980), the abortion incidence due to EHV-1 has remained relatively constant, between 2 and 2.5 abortions per 1,000 pregnant mares." An abortion storm can occur at any time, sweeping through an entire farm with disastrous results.

Similarly within the central nervous system, blood vessel damage results in cellular death of neurons, with variable neurologic deficits related to specific areas of damage. An affected horse is overtaken suddenly with ascending paralysis that usually peaks to its worst state within two to three days of onset. Telltale signs of paralytic

rhinopneumonitis are poor tail tone along with fecal incontinence and urinary leakage due to partial or complete bladder paralysis. The hind limbs become weak or hind limb coordination falters (ataxia), usually in a symmetrical fashion. Many horses afflicted with paralytic rhinopneumonitis go down and remain recumbent with the effects of the infection lasting for three weeks or more.

Breathnach notes, "The incidence of EHV-1 neurologic disease in the field is presumably low, even allowing for the fact that many neurologic cases may be mild and self-limiting. Again, however, some strains can apparently induce severe neurological deficits in a very high percentage of exposed animals. How do they arise? What confers this enhanced virulence? This is a hot-button issue in EHV-1 research."

As research strives to answer these questions, the impact of EHV-1 in a neurologic storm remains a current concern to the horse industry, particularly as more cases arise in locations of congregated horses, such as training barns and racetracks. As an example of the havoc this EHV-1 viral manifestation can cause, we need only turn to the 2003 herpesvirus outbreak in Findlay, Ohio. Of 138 horses in the herd, 124 developed fever and a nasal discharge. Of those, 30 developed neurologic signs and 12 had to be euthanatized. This kind of epidemic outbreak occurs because a horse that is incubating and shedding disease might not demonstrate any clinical signs until it is too late to isolate him.

This virus is highly contagious, it spreads like wildfire in a herd, and it spreads to others elsewhere if a sick horse is moved to another location (such as a veterinary hospital). If an exposed horse does not develop clinical signs within three weeks, the good news is that he probably is not going to become ill.

Vaccination Quandaries

Currently, vaccines are labeled for activity against the respiratory and abortigenic forms of equine herpesvirus, but none are available to counter the neurologic form. Allen, in collaboration with Nicholas Davis-Poynter, PhD, head of equine infectious diseases at the Animal Health Trust in Newmarket, England, has made a recent discovery: "Neuropathogenic isolates of EHV-1 possess a mutation that offers a possible explanation for many of the unique properties of these neurologic strains. For example, it explains the basis for the increased vigor of such isolates to replicate, their ability to cause amplified magnitudes of viremia following infection, their greater capacity to infect cells lining the blood vessels (endothelium), and the relative inefficacy of all current vaccines for preventing infection by such aggressive strains of EHV-1. The core question, as yet without an answer, is whether such neuropathogenic mutants of EHV-1 arise anew with each disease outbreak or whether there exists a subpopulation of horses that carry the mutant strains as latent virus with the potential for initiating new outbreaks of paralytic disease. Such a gene mutation of EHV-1 renders current vaccines ineffective against it."

In addition, no vaccine can protect against latent infection because the virus does not present itself to the horse's immune system when it persists in this silent form. Breathnach's assessment on EHV-1 vaccines is revealing: "In general, the vaccines for EHV-1 are suboptimal. Most of them are inactivated vaccines, which typically induce only circulating antibodies, but do little or nothing to induce cytotoxic T-cell (CTL) activity. EHV-1 gets into the bloodstream and circulates by hiding in lymphocytes and monocytes. It is therefore largely inaccessible to serum antibodies. The virus can then pass directly from infected lymphocytes to vascular endothelial cells lining the blood vessels of the pregnant uterus or central nervous system, further avoiding antibody intervention. If serum antibodies are the only source of immunity in the infected horse, they cannot effectively control spread of the virus to the blood vessel lining (endothelium)."

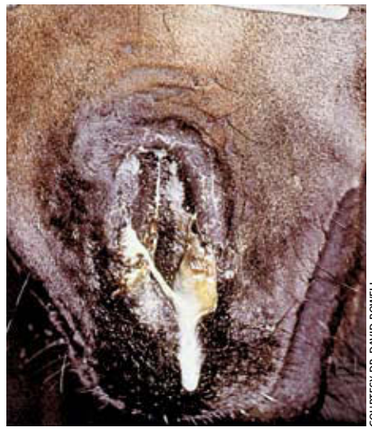
He elaborates about future research possibilities: "What we need are vaccines that induce CTL responses that will kill virus-infected circulating lymphocytes. Use of such vaccines could be expected to reduce the burden of virus in the bloodstream and decrease the risk of spread of virus to vulnerable endothelial cells."

Of available vaccines worldwide, there are killed or "inactivated" forms and "modified live" (MLV) forms. When given intramuscularly, inactivated vaccines stimulate circulating antibodies in the bloodstream, but are not designed to effectively elicit responses at the level of the respiratory lining or within white blood cells of the cell-mediated arm of immune defense. When given intramuscularly, MLV vaccines stimulate circulating antibodies along with a cell-mediated response from white blood cells, but whether immunity is developed in the respiratory lining is debatable.

Breathnach speculates on improvements in vaccine availability in the future: "While vaccination with the currently available products is important, it is clear

BLM FILE PHOTO

Poor nutrition, a heavy parasite load, overcrowding, and rigorous climatic events are just some of the stressors that adversely affect a horse's immune defenses.



COURTESY DR. DAVID POWELL

After several days of infection with equine herpesvirus, the clear nasal discharge turns progressively thicker, leaving a crust around the nostrils. Less than a week into the illness, this turns into a yellowish, snotty discharge due to bacterial invasion of damaged cells lining the repiratory tract.

that improved vaccines are desirable. One thing to keep in mind is that even live virus infection of horses results in relatively short-term protective immunity. Typically a young horse that has had limited exposure to the virus can become sick, recover, then be vulnerable to re-infection within six months. With this in mind, it becomes very difficult to design vaccines that emulate this protective immunity, let alone exceed it. Most likely, the best we can hope for in vaccine design is to create one that is as protective as a live virus infection. To do so, we would have to create a vaccine that stimulates the various arms of the immune response that are activated by live virus infection (far more than just serum antibodies). With inactivated vaccines this is virtually impossible. Our best hope remains MLV vaccines, or recombinant subunit vaccines (where a small component of the virus is inserted into a live—but innocuous—carrier virus for vaccination). However, development of such subunit vaccines has its own caveats. You first have to identify the "immunodominant" (most relevant) protein(s) in the virus for inclusion in the vaccine. In the case of EHV-1, there are about 70 proteins, many of which are good candidates for immunogenicity. Furthermore, there is no guarantee that any single protein will suffice; it might take two or more."

Some horse owners have dug in their heels and won't use herpesvirus vaccines, basing their objection on hearsay about the possibility of MLV vaccination inducing paralytic rhinopneumonitis. Allen puts this outdated concern to rest, saying the following: "The only MLV for EHV-1 currently marketed in the USA is a product that is prepared from a non-neuropathogenic strain of EHV-1 and has been used for many years without any indication of causing either paralysis, abortion, or even respiratory disease. The concern about MLV and paralysis probably is a holdover from the use of a neuropathogenic mutant in the 1970s, which did result in a large number of paralytic cases in vaccinates."

Breathnach concurs, saying, "Given my experiences, the potential of the currently available MLV herpesvirus vaccine to induce secondary complications like neurological disease is infinitesimally small."

To Vaccinate, and With What?

The argument over equine herpesvirus vaccination is controversial. Some maintain that since at least half of the horse population has already been exposed to equine herpesvirus, then vaccination cannot prevent disease, so why bother?

Even with vaccines for EHV-1 that are currently available, there are sound reasons to implement a vaccination protocol. Foremost is to diminish the level of viremia for horses that have not been previously exposed or in those in which latent infection is reactivated. Both at the time of initial exposure and during reactivation of a latent infection, the presence of local immunity within the respiratory lining determines the outcome: If a horse had previous exposure and infection, or if the horse had received vaccination, then his body will have mounted some sort of immune response. Subsequently, sufficient antibody could be present within the lining of the respiratory surface to neutralize reactivated virus. Then, the infective process would be stopped in its tracks before nasal secretions could shed virus to others within a herd.

Breathnach states, "One of the main functions of vaccination and serum antibody elevation is that it may reduce the amount and/or duration of virus shedding. So, increasing herd immunity by vaccination is a valid attempt to restrict the virus burden in the environment."

The role of vaccination is not to eliminate latent infections, but rather to stimulate immunity to a state of readiness to neutralize reactivated virus. This keeps herd health at its best.

The objective in stimulating immunity is to eliminate virus before it can enter the cells or restrict the spread of virus thereafter. Currently, the most effective control of respiratory infection lies at its site of entry—the upper respiratory lining. Based on this strategy, intranasal inoculation is particularly beneficial to limit viral respiratory disease. Immunity provided by intranasal vaccine lasts from three to six months.

When to Vaccinate?

The recommended protocol for protecting pregnant mares against equine herpesvirus abortion is to administer herpesvirus vaccine prior to breeding, then at five, seven, and nine months of gestation. For this purpose, it is best to use those herpesvirus vaccines labeled specifically for pregnant mares. Currently, these are inactivated vaccine products, given as an intramuscular injection.

Most initial cases of herpesvirus infection occur from weaning age to 12 months, and it is speculated that 80-90% of young horses will have been infected by two years of age. If a young horse encounters herpesvirus for the first time when he's over a year of age, he is likely to develop a serious bout of infection. In light of these facts, the best immunization strategy is based on vaccination of young horses. Up until three to five months of age, a foal is unlikely to respond to vaccination due to blockage from maternally derived antibodies of passive transfer that came from a mare's colostrum, particularly if she was vaccinated prior to foaling.

Allen says that vaccination titers are highest when a foal receives its first immunization at five months of age or older. A series of three immunizations should be administered to start a young horse on a herpesvirus vaccine program. For the best effect, all horses (young and old) within a herd should be properly immunized. Many vaccines target both EHV-1 and EHV-4. An adult horse should receive boosters at three- to six-month intervals; the frequency is dependent on the risk of exposure and the risk of stress-related travel and competition. In all cases, immunize according to manufacturer's labels.

ABOUT THE AUTHOR

Nancy S. Loving, DVM, *owns Loving Equine Clinic in Boulder, Colo., and has a special interest in managing the care of sport horses. An enthusiastic endurance rider, Loving is also a veterinary judge for the American Endurance Ride Conference and for FEI (international) endurance events. She authored the books* Go the Distance: The Complete Resource for Endurance Horses, Conformation and Performance *(both available at www.ExclusivelyEquine.com or by calling 800/582-5604), and* Veterinary Manual for the Performance Horse.