

Vaccination Programs for Foals and Weanlings

W. David Wilson, BVMS, MS

Absorption of maternal antibodies from colostrum is important for protection of foals against specific infectious diseases but also substantially interferes with the response of foals to many vaccinal antigens. It is now well documented that the response of foals from vaccinated mares to inactivated influenza vaccines is blocked until at least 6 months of age, and administration of influenza vaccines at an earlier age may induce tolerance, resulting in a negligible response to influenza vaccines administered later in life.¹⁻⁶ Most foals from vaccinated mares fail to respond serologically to common vaccinal antigens when primary immunization is started at 3 months of age, even when three doses of vaccine are administered in the primary series.² In the case of EHV-1, EHV-4, WEE, EEE, and tetanus, preliminary results suggest that administration of vaccines to 3-month-old foals with detectable levels of maternal antibody does not negatively impact their response to subsequent doses of vaccine administered after maternal antibody levels have declined.^{2,7} However, more consistent responses to these antigens are achieved if primary immunization is delayed until 6 months of age or older. Since foals are frequently exposed to EHV-4, EHV-1 and, in the southeastern states, EEE during the first 6 months of life, it is rational to commence vaccination against these diseases at less than 6 months of age only if the risk of infection is high. Administration of inactivated influenza vaccines should be delayed until foals from vaccinated mares are at least 6 months of age and, preferably, 9 months of age or older. Regardless of the age at which foals are first vaccinated and the inactivated vaccine to be used, at least three doses of vaccine, rather than the two recommended by most vaccine manufacturers, appear to be necessary for primary immunization.² Author's address: Dept. of Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis, CA 95616. © 1999 AAEP.

1. Introduction

Vaccination of horses is widely practiced and forms an important part of infectious disease control programs. These programs necessarily start with recommendations for primary immunization of foals, the major goals of which are either protection of foals against diseases they are likely to encounter during the first year of life or initiation of a program for protection of the individual later in life. Foal vaccination practices vary substantially between different parts of the world reflecting tradition, the

likelihood of challenge with a particular infectious agent, and limited research data. For instance, in England vaccination of foals is generally not initiated until 6 months of age or older, at which time vaccination against tetanus and influenza usually commences with bivalent inactivated vaccines containing tetanus and influenza antigens. In the United States, vaccines are available to immunize horses against a large number of diseases, including tetanus, eastern equine encephalomyelitis (EEE), western equine encephalomyelitis (WEE), Venezu-

NOTES

Table 1. Sample Vaccination Schedule for Breeding Farms in the Western United States.^a

1. Booster vaccinate mares in endemic areas against rabies (and EVA if risk exists) before breeding.
2. Booster vaccinate mares against tetanus, WEE, EEE, influenza, EHV-1/4, (strangles), (botulism), and (rotavirus) 4 to 6 weeks before foaling.
3. Vaccinate foals as follows:
4 months—EHV-1/4, (strangles)
5 months—EHV-1/4, (strangles)
6 months—Tetanus, WEE, EEE, (rabies)
7 months—Tetanus, WEE, EEE, EHV-1/4, (Strangles)
8 months—(rabies), (EVA)
9 months—Influenza, tetanus, WEE, EEE
10 months—Influenza, EHV-1/4
1 year—Influenza, (strangles)
4. Thereafter:
Tetanus, WEE, EEE, and (rabies) boosters annually
Influenza and EHV-1/4 boosters at 4-month intervals
(Strangles) boosters at 6-month intervals

^aDiseases listed in parentheses are included in the program only when conditions of significant risk prevail or when indicated for other reasons. In Southeastern states where EEE is a risk year-round, vaccination against EEE and WEE should commence at 4 months of age. Additional vaccines such as botulism, rotavirus, or PHF can be added to the program if endemic conditions exist.

elan equine encephalomyelitis (VEE), influenza, equine herpesvirus 1 (EHV-1), equine herpesvirus 4 (EHV-4), strangles, rabies, Potomac horse fever (PHF), rotavirus, botulism, and anthrax. Because of the paucity of published studies to evaluate foal vaccination, recommendations for primary vaccination of foals using many of these antigens are largely empirical or are based on unpublished data generated by vaccine manufacturers.

Labels on most commercially available vaccines either give no indication as to the appropriate age to

begin vaccinating foals or state that healthy horses more than 3 months of age or more than 9 months of age can be vaccinated. In 1995 the AAEP Committee on Biologic and Therapeutic Agents published guidelines for vaccination of horses that suggested vaccination of foals for most antigens except for influenza, at 3 to 4 months of age.⁸ However, the high incidence of pneumonia and other respiratory diseases in foals has prompted practitioners to intensively vaccinate foals against influenza, EHV-1, and EHV-4 beginning as early as 1 month of age. The literature contains very few published studies to investigate serological responses in foals to commonly used vaccines, and even fewer studies in which the serologic responses of foals to vaccines have been validated by challenge studies to document that suggested vaccination guidelines actually induce protection. In recent years, several studies have documented the failure of a high proportion of foals from vaccinated mares to respond serologically to inactivated influenza vaccines administered at less than 6 months of age.^{1,3-6} These findings have called into question foal vaccination protocols directed against antigens other than influenza and have highlighted the lack of published reports. In this presentation, I will attempt to clarify the issue through review of available published information and limited data from as yet unpublished studies completed in our laboratory and elsewhere.

To maximize passive protection foals and maximize the uniformity of colostral antibody transfer within the foal crop, it is important to maintain broodmares on a regular vaccination program and administer booster doses of appropriate vaccines 4 to 6 weeks before foaling. Under these circumstances, most foals acquire serum titers of specific antibody very similar to those present in the mare. For most

Table 2. Vaccination Recommendations for Foals, Weanlings, and Foaling Mares.

	Mare 4-6 Weeks Prefoaling	Foal							
		4 mo	5 mo	6 mo	7 mo	8 mo	9 mo	10 mo	12 mo
Influenza	X						X	X	X
EEE ^a	X	*	*	X	X*		X		
WEE ^a	X	*	*	X	X*		X		
Tetanus	X			X	X		X		
EHV-4	X	X	X		X			X	
EHV-1	X	X	X		X			X	
Rotavirus	X (8, 9, 10) ^b								
Botulism	X (8, 9, 10) ^{b,c}								
Rabies ^d				X			X		
Strangles ^e	X	X	X		X				X
EVA ^d							X		

Vaccines in the shaded block are only indicated in endemic areas or farms on which the risk of infection is high.

^aRecommendations for EEE/WEE vaccination in Southeastern states with year-round risk of EEE infection are indicated with an asterisk *, whereas recommendations for the remainder of the US are indicated with an X.

^bNumbers indicate the month of pregnancy when vaccination is indicated.

^cFor mares that have been vaccinated against botulism in previous pregnancies, administer a single booster dose 4-6 weeks before foaling.

^dRabies and EVA boosters for mares should be administered pre-breeding.

^eStrangles recommendations apply only to injectable vaccines.

IN DEPTH: PEDIATRICS

of the diseases investigated to date, concentrations of passively acquired antibodies in the circulation of the foal decline with a half-life of 30 to 40 days.^{3,4,7,9} Depending on the level of antibodies absorbed and characteristics of the specific infectious agent, passively derived colostral antibodies may protect the foal from specific infectious diseases for a period ranging from a few weeks to several months. As well as neutralizing infectious agents, passively derived antibodies can also bind the modified antigens present in vaccines, resulting in a reduction or elimination of their ability to induce a protective immune response, a phenomenon termed "maternal antibody interference." It appears that small amounts of antibody, below levels thought to be protective, can induce complete maternal antibody block, resulting in a sometimes prolonged period of susceptibility between the time colostral antibodies decline to below a protective level and before the foal is able to mount a response to vaccination.²

When deciding how to approach the use of vaccines in foals it is important to decide which one of the following is the most important goal or whether both are equally important:

- a. To protect the foal and weanling against specific high-risk infectious diseases that affect this age group and have the potential to cause significant disease, either directly or by predisposing to other secondary infections, or
- b. To initiate primary immunization to protect against disease later in life.

Therefore, one of the first questions that should to be answered is: "What risk does this disease pose to the foal or weanling?" Assessing risk takes into account both the incidence of disease (i.e., the likelihood that the foal will become infected) as well as the risk of serious sequelae or death if the horse does become infected. If the disease affects the foal early in life, such as is the case with rotavirus infection, there is usually insufficient time to induce a protective immune response by actively immunizing the foal. Under these circumstances, the approach should be to maximize the degree of protection passively transferred from the dam via colostrum. Other diseases, such as rabies, affect horses of all ages, but the risk of acquiring infection is generally low. On the other hand, horses of all ages are susceptible to herpesvirus infection and the risk of encountering infection is relatively high. Furthermore, the severity of disease and risk of death are important considerations, even for rare diseases. For example, tetanus and rabies are relatively uncommon diseases that are often fatal, whereas influenza is a relatively common disease that is rarely fatal.

Diseases of high risk to young foals but low risk to adults include rotavirus infection (on certain breeding farms in certain years) and, in geographic areas such as Kentucky and some other Eastern states,

botulism. For these diseases the best approach is to:

- a. Booster vaccinate the dam before foaling to maximize uniformity of passive transfer.
- b. Ensure good passive transfer of maternal antibodies.
- c. Introduce management practices to reduce exposure to the infectious agent.
- d. Vaccinate the foal if risk continues beyond first few months of life.

Diseases of moderate to high risk for weanlings and older horses but lower risk to young foals born to vaccinated mares include EHV-4, EHV-1, strangles, influenza, tetanus and, in the eastern United States, EEE. For these diseases the best approach is to:

- a. Vaccinate the dam before foaling to maximize uniformity of passive transfer.
- b. Ensure good passive transfer of maternal antibodies.
- c. Start foal vaccination after the risk of maternal antibody interference is no longer present in *most* foals, as long as it has been ascertained that vaccination in the face of maternal antibodies does not impair the ability of foals to respond when vaccinated later in life (i.e., tolerance).
- d. Introduce management practices to reduce exposure to the infectious agent while primary vaccination is being completed.
- e. Use three or more doses of vaccine in the primary series to improve the chances that foals that did not respond to earlier doses will respond when given additional doses later.

Diseases of low risk to foals in most circumstances include rabies, PHF, WEE, equine viral arteritis (EVA), and anthrax. For these diseases the best approach is to:

- a. Vaccinate the dam before foaling if the disease is a significant risk to adult horses and a vaccine approved for use in pregnant mares is available. If a vaccine is not approved for use in pregnant mares, administer boosters before breeding.
- b. Ensure good passive transfer of maternal antibodies.
- c. Start foal vaccination after the risk of maternal antibody interference is no longer present in *any* foal.

A. Recommendations for Vaccination Against Specific Diseases (Tables 1 and 2)

The recommendations below refer to vaccines currently available for use in horses in the United States and are based on limited available research data. In many instances results are based on serologic responses to vaccination, not documented protection in challenge studies. These recommendations will likely require adjustment as more informa-

tion becomes available. It is possible that for some diseases, lack of a serologic response may correlate well with lack of protection, whereas for others, this may not be the case. On the other hand, the presence of a serologic response may not correlate well with protection, as is frequently the case for respiratory tract pathogens. With the exception of the intranasally administered strangles vaccine (Pinnacle I.N., Fort Dodge), the modified live virus EHV-1 vaccine (Rhinomune, Pfizer), and the modified live virus EVA vaccine (Arvac, Fort Dodge), most commercially available vaccines are inactivated, adjuvanted, and administered by intramuscular injection. As such, they are much more likely to induce a systemic serologic response than either a cell-mediated immune response or local mucosal immunity.

2. Rotavirus Infection

Rotavirus infection causes diarrheal illness in foals during the first few weeks of life. Older foals and adult horses are more resistant to infection. The major goal of a rotavirus vaccination program is therefore to reduce the risk of serious rotaviral diarrhea in foals during the first few weeks of life. The major correlate for protection against rotaviral diarrhea appears to be mucosal immunity in the gastrointestinal tract, either induced by recovery from infection or passively acquired from colostrum and milk during nursing. Parenteral vaccination of the dam before foaling does not guarantee protection of the foal but has been shown to reduce the incidence and severity of disease in foals born to vaccinated mares.¹⁰⁻¹² A commercially available inactivated vaccine (Rotavirus Vaccine, Fort Dodge) is conditionally licensed for IM use in many states and, while not completely effective in preventing infection, appears to reduce the incidence and severity of disease in the field setting.¹⁰ The recommended program for the use of rotavirus vaccine is as follows:

- a. Vaccinate the dam during 8th, 9th, and 10th month of gestation.
- b. Repeat the three-dose vaccination series during each subsequent pregnancy
- c. Foal vaccination is not indicated

3. Toxicoinfectious Botulism: "Shaker Foal Syndrome"

Of the eight distinct toxins produced by subtypes of *Clostridium botulinum*, types B and C are associated with the majority of botulism outbreaks, and virtually all cases of toxicoinfectious botulism (shaker foal syndrome) are caused by type B.¹³ Shaker foal syndrome is an important problem affecting foals between 2 weeks and 8 months of age in Kentucky and the mid-Atlantic states and occurs sporadically in other areas.¹³ A *C. botulinum* type B toxoid vaccine (Bot-Tox-B, Neogen) is available with the primary indication being the prevention of shaker foal syndrome in endemic areas. Antibodies against

toxin type B do not cross-protect against other toxin types. Protection appears to be mediated primarily by circulating antibodies since a program of mare vaccination has been shown to offer protection to foals that achieve good passive transfer of colostral antibodies, which protect the foal for 8 to 12 weeks.^{13,14} The recommended program for the use of Bot-Tox-B is as follows:

- a. Vaccinate the dam during the 8th, 9th, and 10th months of gestation.
- b. Vaccinate the dam 4 to 6 weeks before foaling in subsequent pregnancies.
- d. Vaccinate the weanling at 3 months of age or older if the risk of infection continues.

Vaccination of foals and weanlings is usually not indicated and there are no published data to determine whether maternal antibodies interfere with the response of 3-month-old foals to vaccination.

4. Equine Herpesvirus Type 1 (EHV-1) Infection

The major concern with EHV-1 infection, and the only syndrome for which good efficacy has been documented, is prevention of EHV-1 abortion in mares. Both of the vaccines approved for this purpose (Pneumabort K + 1b, Fort Dodge and Prodigy, Bayer) are inactivated and administered by the IM route. A modified live virus vaccine (Rhinomune, Pfizer) has been used by some practitioners for many years but does not carry an approved claim to prevent EHV-1-associated abortion. The recommended protocol for the use of approved inactivated vaccines is to vaccinate mares during the 5th, 7th, and 9th months of every pregnancy. Vaccination of foals and weanlings against EHV-1 infection is addressed below.

5. Equine Herpesvirus Type 4 (EHV-4) and EHV-1 Infection

Equine herpesvirus type 1 and EHV-4 infect the host via the respiratory tract after inhalation or ingestion of infective aerosols or direct contact with infected horses or products of EHV-1 abortion. Whereas viremia frequently occurs after infection with EHV-1, leading to myeloencephalopathy, abortion, or birth of infected nonviable foals, manifestations of infection with EHV-4 (rhinopneumonitis) are generally confined to the respiratory tract because EHV-4 does not infect endothelial cells or produce a cell-associated viremia.¹⁵ Horses frequently become infected with EHV-4 and EHV-1 during the first year of life and develop clinical signs of respiratory disease but fail to clear the virus, resulting in a chronic carrier state in the majority of the horse population. Infection may recrudesce later in life as a clinically apparent or inapparent infection resulting in an increase in serum neutralizing antibody titers. Consequently, many horses have detectable levels of SN antibody to both EHV-1 and EHV-4 in their serum.

Correlates for protection against EHV-1 and EHV-4

IN DEPTH: PEDIATRICS

infection have been extensively investigated but are not yet clearly defined.¹⁵ Infection with EHV-1 induces a strong humoral response, but protection from reinfection is short-lived and is not achieved until the horse has experienced multiple infections with homotypic virus.¹⁵ No clear relationship exists between protection from EHV-1 infection and levels of circulating antibody induced by vaccination or infection, but the duration and amount of virus shedding from the nasopharynx is reduced in animals with high levels of circulating neutralizing antibody.¹⁵ As with other herpesviruses, mucosal immunity and cell-mediated responses likely play a role at least as important as circulating neutralizing antibodies in protection against EHV-1 infection. Evidence for the role of CMI comes from studies demonstrating that the presence of MHC class 1 restricted cytotoxic T-lymphocyte precursors in peripheral blood are correlated with protection.¹⁵ Because EHV-4 replication is largely confined to epithelial cells of the upper respiratory tract, it is likely that mucosal immunity is important in protection.¹⁵ Whereas circulating antibodies alone do not prevent EHV-4 infection, high levels of vaccine-induced circulating VN antibody markedly reduce virus shedding and clinical signs after challenge infection.¹⁵

Specific antibodies to both EHV-1 and EHV-4 are passed in colostrum.¹⁶⁻¹⁹ Field studies with modified live EHV-1 vaccines indicate that colostral antibodies exert a profound inhibitory effect on serologic responses to vaccination up to at least 5 months of age.¹⁹⁻²¹ However, a cytotoxic cellular immune response to both EHV-1 and EHV-4 was induced in a substantial percentage of foals vaccinated with a modified live EHV-1 vaccine in the presence of maternal antibody, even though humoral responses were often absent.²² Recent studies with two different commercially available inactivated bivalent EHV-1/4 vaccines, and one inactivated EHV-4/influenza vaccine, have shown that the majority of foals from EHV-vaccinated mares do not mount a detectable neutralizing antibody response to vaccines administered at 3 and 4 months of age, even when three doses are administered in the primary series.^{2,16,17} An increased proportion of foals responded when vaccinated with a three-dose series starting at 5 or 6 months of age, but still a substantial number failed to seroconvert.^{2,16} Some foals with low or undetectable levels of SN antibody at the time of vaccination failed to mount a serologic response.^{2,16} It appears that either levels of antibody below the limit of quantitation of the serum neutralization test may interfere, or that some foals do not respond to inactivated EHV-1/4 vaccines, regardless of the presence or absence of neutralizing antibody. Data from a small number of foals suggest that for EHV-1 and EHV-4, vaccination in the presence of detectable maternal antibodies does not render them tolerant to subsequent doses of vaccine or to field challenge.²

The obvious dilemma in designing a vaccination

strategy to prevent EHV-1 and 4 infection in foals and weanlings is that if primary immunization is delayed until 6 months or more in age, when maternal antibody titers have declined to low levels and are less likely to interfere with vaccination, foals are likely to encounter field infection before completion of the three-dose primary series. Thus, it is unreasonable to expect a high degree of efficacy in vaccination programs designed to protect foals and weanlings against EHV infection using available vaccines. Under circumstances where vaccination of foals against EHV-1 and EHV-4 is elected, the following compromise program may be used:

- a. Vaccinate the dam 4 to 6 weeks before foaling with an inactivated bivalent EHV-1/4 vaccine.
- b. Start foal vaccination at 4 to 6 months of age with two doses of an inactivated bivalent vaccine or modified live EHV-1 vaccine administered 3 to 4 weeks apart with a third dose administered 6 to 8 weeks later.
- c. Booster vaccinate at 3- to 4-month intervals

6. Tetanus

Regular vaccination against tetanus has been a central component of recommended immunization programs for horses for many years. As a result, tetanus is now rarely encountered as a clinical entity in horses. Protection against tetanus appears to be mediated entirely by circulating antibodies and these antibodies are transferred well via colostrum.^{2,23} Thus, foals born to vaccinated mares appear to be at low risk of developing tetanus. Limited and conflicting information is available in the literature regarding the potential for maternal antibody interference with vaccination. Based on available published results, Liu (1986) recommended primary vaccination of foals against tetanus starting at 4 to 6 months of age.²⁴ Tetanus toxoid is considered to be a potent antigen, and it has been widely accepted that concurrent administration of tetanus toxoid and antitoxin at different sites does not interfere with the response to tetanus toxoid.^{8,25} Consequently, it has been assumed that maternal antibodies were unlikely to interfere with the response of foals to tetanus toxoid. However, recent studies indicate that the response of 3-month-old foals from vaccinated mares is substantially poorer than the response of 6-month-old foals and yearlings.² In addition, these studies show that levels of induced antitetanus antibodies were substantially higher after administration of a third dose of vaccine than after two doses of vaccine, even in older foals. The following protocol appears to be appropriate for tetanus vaccination:

- a. Vaccinate the dam 4 to 6 weeks before foaling.
- b. Begin foal vaccination at 6 months of age.
- c. Administer three doses of tetanus toxoid in the primary series.
- d. Booster vaccinate at 12-month intervals thereafter.

7. Strangles

Strangles vaccination is indicated for horses likely to experience a substantial risk of exposure, such as those being introduced to or born onto premises where strangles is endemic. Protection against *Streptococcus equi* infection appears to be mediated by a combination of mucosal IgG and IgA antibodies produced locally in the nasopharynx and opsonic IgG antibodies in serum.²⁶⁻²⁸ Until recently, available strangles vaccines were either inactivated whole cell vaccines (Equibac II, Fort Dodge) or M-protein cell wall extracts (Strepvax, Boehringer Ingelheim, Strep-guard, Bayer). These vaccines induce a good opsonophagocytic antibody response in serum but minimal mucosal response, which likely accounts for the incomplete protection observed when these vaccines are used in the field.²⁷ However, data do exist to document that vaccination using injectable M-protein vaccines significantly reduces the attack rate and severity of strangles in herds with endemic infection.²⁹⁻³¹ Recently, an attenuated live vaccine (Pinnacle I.N., Fort Dodge) for intranasal administration was introduced onto the market and is now in widespread use. Vaccines of this type have been shown to induce a relevant mucosal immune response and partial or complete protection.³²

Antibodies of the IgG and IgA class recognizing the M-protein of *S. equi* are passively transferred to the foal via colostrum and are also present in the milk of immune mares.³³ IgA class antibodies absorbed from colostrum recirculate to the nasopharyngeal mucosa and, along with milk antibodies that passively coat the pharyngeal mucosa, provide protection to most nursing foals up to the time of weaning.²⁶ Serologic (ELISA) responses to M-protein vaccines are poor in foals, most likely due to the inhibitory effect of maternal antibodies, although no evidence has been presented to suggest that vaccination against strangles in the face of maternal antibodies induces tolerance. The modified live intranasally administered vaccine may be less subject to interference from circulating maternal antibodies. However, this issue has not been investigated and the manufacturers do not recommend administration of this vaccine to horses less than 9 months of age. The following vaccination protocol appears rational on breeding farms on which the risk of strangles infection is high and mares are on a regular vaccination program:

- a. Booster vaccinate the dam 4 to 6 weeks before foaling using an inactivated M-protein vaccine.
- b. Begin foal vaccination at 4 to 6 months of age with an intramuscularly administered M-protein vaccine, using at least three doses in the primary series, followed by boosters at 6-month intervals.
- c. Alternatively, begin foal vaccination with the intranasal live vaccine at 6 to 9 months of age using the recommended two-dose primary series followed by boosters at 6- to 12-month intervals.

8. Influenza

Infection with influenza A-equine-2 virus is a common cause of rapidly spreading outbreaks of respiratory disease in North America and Europe. Although horses of all ages are susceptible, young performance and show horses appear to be at the greatest risk of acquiring infection because they have a high likelihood of contact with horses and they are likely to be encountering the virus for the first time. Horse populations on breeding farms would also be expected to be at high risk because of the high "traffic" in horses from different sources and the high proportion of young susceptible animals. Despite these epidemiological considerations and the commonly held belief that influenza is an important predisposing factor to the high incidence of pneumonia in foals, documented outbreaks of influenza in foals residing on breeding farms on which adults are regularly vaccinated against influenza are rare. Therefore, the indication for vaccination of young foals against influenza is likely much lower than commonly believed.

Immunity following natural infection with influenza persists for more than 1 year and is not dependent on high levels of circulating antibody.^{15,34,35} In reinfection experiments, ponies in which titers of circulating antibody had declined to low or undetectable levels postinfection resisted challenge more than 1 year after initial infection.³⁵ In addition to invoking a strong serologic response, natural infection induces large amounts of virus-specific secretory virus neutralizing IgA in nasal secretions and genetically restricted cytotoxic T lymphocytes (CTL) that kill infected cells.^{15,34} Memory CTL can be detected in the peripheral blood for at least 6 months after infection.¹⁵ In contrast, immunity following vaccination with conventional parenterally administered inactivated vaccines is short lived and is highly correlated with levels of circulating antibody directed against surface hemagglutinin antigens.^{34,36} With the possible exception of ISCOM vaccines, conventional vaccines have limited potential to induce CTL responses or nasal secretory IgA responses.³⁴

Conclusive evidence was presented almost 10 years ago documenting that hemagglutination inhibition (HI) antibodies against both influenza A-equine-1 and A-equine-2 were transferred to foals via colostrum and that these antibodies declined with a half-life of approximately 30 to 38 days.³⁴ These workers also demonstrated that the majority of foals from vaccinated mares did not respond to inactivated adjuvanted influenza vaccines administered at 3 months of age, whereas a higher proportion of 6-month-old foals responded if given three doses of influenza vaccine in the primary series.³ Similar observations were made by Cullinane et al.¹ during investigation of the finding that many yearling horses had low or undetectable levels of HI antibody despite having received multiple doses of influenza vaccine during the first year of life. In addition, these

IN DEPTH: PEDIATRICS

workers found that a substantial number of foals vaccinated at less than 6 months of age not only failed to respond serologically to doses of vaccine administered in the primary series but also failed to respond to as many as six doses of vaccine administered over the next year, suggesting that early vaccination in the presence of maternal antibody had induced immunotolerance to influenza vaccines.¹ From these observations it was concluded that foals from vaccinated mares should not be vaccinated against influenza at less than 6 months of age and that three doses of vaccine were necessary in the primary series.^{1,3} These results have recently been confirmed using vaccines available in North America during studies in Kentucky and in California.^{2,5,6} Results indicate that whereas the response of 6-month-old foals is superior to that of 3-month-old foals, both in terms of the percent seroconverting and the magnitude of the resulting titers, the response of yearlings is clearly superior to that of 6-month-old foals.² Whereas 60% of the yearlings seroconverted to influenza A-equine-2 after two doses of vaccine, all seroconverted after three doses and more than 50% developed HI titers of more than 1:1000.² Based on these findings, current recommendations for vaccination against influenza using inactivated vaccines administered by intramuscular injection are as follows:

- a. Maintain all horses on breeding farms on a program of booster vaccination against influenza at 4- to 6-month intervals.
- b. Booster vaccinate mares 4 to 6 weeks before foaling.
- c. Begin foal vaccination at 6 to 12 months of age using three or more doses in the primary series.
- d. Booster vaccinate young horses at 3- to 4-month intervals until they are 2 years of age if risk of infection remains high.
- e. Mature performance, show, and pleasure horses constantly exposed to potential infection should be booster vaccinated at 4- to 6-month intervals.

9. Western, Eastern (and Venezuelan) Equine Encephalomyelitis

Correlates for protection against WEE and EEE are not well established, but because natural infection is acquired by injection (mosquito bites) and current inactivated vaccines appear to be protective, it is assumed that circulating antibodies are important for protection. Neutralizing antibodies to WEE and EEE are passively transferred to foals via colostrum and are detectable in the serum of many foals from vaccinated mares for at least 3 months.^{7,37} The half-life of decline of colostrally derived antibodies against EEE and WEE have been estimated to be 33 and 20 days, respectively.^{7,37} It has been demonstrated that foals vaccinated soon after birth with an inactivated EEE vaccine fail to mount a serologic response and are rendered tolerant to subsequent

doses of vaccine administered later in life.³⁸ Similar studies in older foals showed that, whereas the serologic response to vaccination may be blocked by maternal antibodies, these foals were not rendered tolerant to doses of vaccine administered later in life.⁷ Recent studies comparing the response of 3-month-old foals and 6-month-old foals demonstrated that 3-month-old foals consistently failed to mount a serologic response to two doses of inactivated bivalent WEE/EEE vaccine and the majority had not responded even after three doses.² Whereas most 6-month-old foals fail to respond to two doses of vaccine, the majority seroconverted after administration of three doses.²

EEE is considered to be a significant risk during the summer months in the Eastern United States and a year-round risk in the Gulf States and Florida.³⁹ Since EEE is a highly fatal disease, foals in these areas are considered to be at risk for infection and death during their first year of life.^{7,38} Therefore, vaccination of foals against EEE is recommended in these areas. The efficacy of vaccination programs to prevent EEE have, however, been brought into question by the finding of clinical EEE in vaccinated horses, particularly those less than 2 years of age.³⁹ This finding suggests that vaccine failure may result from interference by colostrally derived antibodies.^{7,38,39}

WEE has a lower mortality than EEE and occurs in Midwestern and Western states, where the risk of infection is highest during the summer and early fall. In most areas, prevalence of WEE infection is low, so the risk of foals acquiring infection during their first year of life is generally low. For this reason, vaccination against WEE can be delayed until the spring of the yearling year in most areas of the Western United States, except in regions where a high prevalence exists. VEE has not been recorded in the United States for many years, although outbreaks have occurred in southern Mexico during the last decade. Vaccination against VEE is not currently recommended except possibly in regions adjacent to the Mexican border. Currently encephalomyelitis vaccines are either bivalent, containing WEE and EEE inactivated antigens (Encevac, Bayer; Encephaloid, Fort Dodge; Cephalovac EW, Boehringer Ingelheim) or trivalent containing WEE, EEE, and VEE (Cephalovac VEW, Boehringer Ingelheim).

Based on current knowledge, the following vaccination protocol for encephalomyelitis is an appropriate compromise:

- a. Booster vaccinate the dam 4 to 6 weeks before foaling.
- b. Begin foal vaccination at 6 months of age or during the spring of the yearling year using three doses in the primary series and booster vaccinate annually thereafter.
- c. In the Southeastern United States, where the risk of EEE infection is high year-round, start vaccinating foals at 4 months of age and use three or more doses in the primary series.

10. Rabies

Correlates for protection against infection with rabies virus in horses are not well defined. Because infection with rabies virus is usually acquired by systemic injection via bites by rabid animals, it is logical to assume that protection would correlate with titers of circulating antibody. In humans postvaccination antibody titers are used to predict protection and to assess the need for postexposure vaccination or administration of immune serum. In dogs, however, postvaccination serologic test results were not found to be predictive of resistance to challenge exposure during tests performed with certain inactivated vaccines.²³ Published results of challenge studies to assess efficacy of rabies vaccines in horses are not available.

No published reports are available concerning passive transfer of maternal antibodies against rabies to foals and the effect of these antibodies on the response of foals to vaccination. This issue is currently under investigation. Label directions on inactivated rabies vaccines approved for use in horses (Rabvac 3, Fort Dodge; RM Imrab3, Rhone Merieux; and Rabguard TC, Pfizer) suggest that these can be administered to foals aged 3 months or older using one dose of vaccine in the primary series followed by a second dose at 1 year of age. The efficacy of this approach has not been evaluated in published challenge studies. Rabies has been documented in reportedly vaccinated horses, most of which were less than 2 years of age.⁴⁰ This finding suggests that current rabies vaccination guidelines may not be uniformly protective. In addition, rabies vaccine is the only inactivated vaccine approved for use in horses for which only one dose is recommended in the primary series. None of the available rabies vaccines carries a label approval for use in pregnant mares. Pending results of research studies, the following approach is recommended for the use of inactivated rabies vaccines in horses in rabies-endemic areas:

- a. Vaccinate the dam *before* breeding.
- b. Begin foal vaccination at 6 months of age or older using two doses in the primary series.
- c. Booster vaccinate as yearlings and then annually thereafter.

11. Potomac Horse Fever (PHF)

Recovery following natural infection with *Ehrlichia risticii* induces a strong antibody response and durable protection from reinfection lasting as long as 20 months.⁴¹ However, presence of antibodies *per se* does not necessarily correlate with protection and it is likely that cell-mediated responses play a crucial role.⁴² Several inactivated PHF vaccines for IM administration (Mystique, Bayer; RM Potomavac, Rhone Merieux; PHF-Vax, Schering-Plough; PotomacGuard, Fort Dodge) are available and carry label claims that they aid in prevention on equine monocytic ehrlichiosis. However, an epidemiologi-

cal investigation involving a large number of horses in New York state, failed to demonstrate any clinical or economic benefit from annual vaccination with currently available vaccines.⁴³ Failure of a substantial number of individual horses to mount an immune response to inactivated PHF vaccines, heterogeneity of *Ehrlichia risticii* isolates, and much more rapid waning of protective immunity following vaccination than after natural infection likely account for vaccine failure.^{44,45} Despite the above findings, many practitioners and horse owners believe that available vaccines do offer some protection when administered at 4- to 6-month intervals, and one study did demonstrate partial protection induced by a commercially available vaccine.^{42,46}

A study of antibody-positive mares and their foals on a farm in Maryland showed that antibodies to *Ehrlichia risticii* were passed via the colostrum and persisted in the serum of about 33% of foals for up to 20 weeks, whereas 67% of foals were antibody-negative by 12 weeks of age.⁴⁷ On the basis of these findings, and the apparent susceptibility to infection of two foals vaccinated earlier than 12 weeks of age, the authors recommended that vaccination of foals from antibody-positive dams should begin at 3 to 5 months of age, followed by administration of one subsequent booster dose.⁴⁶ However, the efficacy of this recommendation requires further study. Vaccination of foals in endemic areas is further complicated by the distinct seasonal incidence of disease in July, August, and September, a time when the majority of foals are aged between 3 and 6 months.

Vaccination of foals against PHF is only indicated in endemic areas, and the efficacy of vaccination protocols for foals has not been proven. Pending results of further studies, the following protocol is generally followed:

- a. Booster vaccinate the dam 4 to 6 weeks before foaling.
- b. Begin foal vaccination at 3 to 5 months of age or older using a three-dose primary series.
- c. Booster vaccinate at 4- to 6-month intervals thereafter.

12. Equine Viral Arteritis (EVA)

Equine viral arteritis is endemic in Standardbred horses, a high proportion of which are seropositive for this disease. The seroprevalence of infection in Thoroughbreds and Quarterhorses is low, although outbreaks of both the respiratory and venereal forms of infection have been documented in Thoroughbred horses during the last 20 years.⁴⁸ Although horizontal transmission of EAV virus during respiratory disease outbreaks is known to be important in propagation of outbreaks, venereal transmission via infected semen during natural cover and artificial insemination using fresh or chilled semen is the most important means of transmission of the virus that maintains it in certain populations of horses.^{48,49} There is good evidence to suggest that a substantial

IN DEPTH: PEDIATRICS

number of Warmblood and Sporthorse stallions imported from Europe are chronic inapparent shedders of this virus in their semen. Establishment of the carrier state appears to be dependent on the high levels of androgens circulating in intact stallions and can be prevented by vaccinating colts, preferably prior to puberty, before they are used for breeding.⁴⁸ Transmission to mares can be prevented by vaccination prior to breeding to a carrier stallion. The modified live virus vaccine (Arvac, Fort Dodge) available for use in the United States has been shown to induce good protection against infection and the development of clinical signs.

Neutralizing antibodies to EVA are passively transferred via colostrum to foals and decline with a mean half-life of 32 days.⁹ In one study, all foals from seropositive mares were found to be negative for antibodies to EVA by 8 months of age, suggesting that this would be an appropriate age to begin primary immunization.⁹ Vaccinated horses can be expected to become seropositive for life, which may complicate export to countries that require serologic testing prior to importation. Maintenance of accurate vaccination records is, therefore, essential. The following protocol is recommended only for horses on breeding farms with a high risk of infection and for mares being bred naturally or by artificial insemination to carrier stallions.

- a. Vaccinate the dam *before* breeding using the modified live vaccine.
- b. Begin foal vaccination at 8 to 10 months of age with one dose of vaccine, followed by annual boosters thereafter.

References

1. Cullinane A, Weld J, Nelly M, et al. The interference of maternal antibodies with the immune response of Thoroughbred foals and yearlings to vaccination against equine influenza, in *Proceedings*. Seventh International Conference on Equine Infectious Diseases 1994;52.
2. Wilson WD, Mihalyi JE. Maternal antibodies interference with the serologic response of foals to conventional vaccines (unpublished observations).
3. van Maanen C, Bruin G, de Boer-Luytze E, et al. Interference of maternal antibodies with the immune response of foals after vaccination against equine influenza. *Vet Q* 1992; 14:13-17.
4. van Oirschot JT, Bruin G, de Boer-Luytze E, et al. Maternal antibodies against equine influenza virus in foals and their interference with vaccination. *J Vet Med B* 1991;38:391-396.
5. Holland RE, Conboy HS, Berry DB, et al. Age dependence on foal vaccination for equine influenza: new evidence from the USA, in *Proceedings*. Eighth International Conference on Equine Infectious Diseases 1998;190.
6. Conboy HS, Berry DB, Fallon EH, et al. Failure of foal seroconversion following equine influenza vaccination, in *Proceedings*. 43rd Annual Convention of the American Association of Equine Practitioners 1997;22-23.
7. Gibbs EPJ, Wilson JH, All BP. Studies on passive immunity and the vaccination of foals against Eastern equine encephalitis in Florida. *Proceedings*, 5th International Conference on Equine Infectious Diseases 1988;201-205.
8. Wilson WD, Kanara EW, Spensley MS, et al. Guidelines for vaccination of horses. The American Association of Equine Practitioners' Vaccination Guidelines Subcommittee of the AVMA Council on Biologic and Therapeutic Agents. *J Am Vet Med Assoc* 1995;207:426-431.
9. Hullinger PJ, Wilson WD, Rossitto PV, et al. Passive transfer, rate of decay, and protein specificity of antibodies against equine arteritis virus in horses from a Standardbred herd with high seroprevalence. *J Am Vet Med Assoc* 1998;213: 839-842.
10. Powell DG, Dwyer RM, Traub-Dargatz JL, et al. Field study of the safety, immunogenicity, and efficacy of an inactivated equine rotavirus vaccine. *J Am Vet Med Assoc* 1997;211: 193-198.
11. Imagawa H, Fujunaga Y, Wada R. Preventive effect against diarrhoea of passive immunity in foals acquired from mares immunised with inactivated equine rotavirus vaccine. *Proceedings*, Eighth International Conference on Equine Infectious Diseases 1998;62.
12. Barrandeguy M, Parreno V, Lagos Marmol M, et al. Prevention of rotavirus diarrhoea in foals by parenteral vaccination of the mares: field trial. *Dev Biol Stand* 1998;92:253-257.
13. Whitlock RH, Buckley C. Botulism. *Vet Clin North Am Equine Pract* 1997;13:107-128.
14. Lewis GE, Kulinski SS, H. FE, et al. Evaluation of a Clostridium botulinum toxoid, type B, for the prevention of shaker foal syndrome, in *Proceedings*. 27th Annual Convention of the American Association of Equine Practitioners 1981;233-237.
15. Hannant D. Respiratory viral diseases of horses: Overview. *Proceedings*, World Equine Airway Symposium 1998;CD ROM.
16. Wilson WD, Rosedale PD. Effect of age on the serological responses of Thoroughbred foals to vaccination with an inactivated Equine herpesvirus (EHV-1/EHV-4) vaccine. *Proceedings*, Eighth International Conference on Equine Infectious Diseases 1998;95.
17. Breathnach CC, Allen GP, Holland RE, et al. Problems associated with vaccination of foals against Equine herpesvirus-4 and the role of anti-EHV-4 maternal antibodies. *Proceedings*, Eighth International Conference on Equine Infectious Diseases 1998;94.
18. Kendrick JW, Stevenson W. Immunity to equine herpesvirus 1 infection in foals during the first year of life. *J Reprod Fertil Suppl* 1979;27:615-618.
19. Burki F, Nowotny N, Rossmannith W, et al. [Training of the immune system of foals against ERP virus infections by frequent vaccination with presently available commercial vaccines]. *DTW Dtsch Tierarztl Wochenschr* 1989;96: 162-165.
20. Dutta SK, Shipley WD. Immunity and the level of neutralization antibodies in foals and mares vaccinated with a modified live-virus rhinopneumonitis vaccine. *Am J Vet Res* 1975;36:445-448.
21. Neely DP, Hawkins DL. A two-year study of the clinical and serologic responses of horses to a modified live-virus equine rhinopneumonitis vaccine. *J Equine Med Surg* 1978;2: 532-540.
22. Ellis JA, Steeves E, Wright AK, et al. Cell-mediated cytotoxicity of equine herpesvirus-infected cells by leukocytes from young vaccinated horses. *Vet Immunol Immunopathol* 1997; 57:201-214.
23. Tizard I, Ni Y. Use of serologic testing to assess immune status of companion animals. *J Am Vet Med Assoc* 1998;213: 54-60.
24. Liu IKM. Duration of maternally derived antibodies in neonatal foals. *Mod Vet Pract* 1986;67:454-456.

25. Liefman CE. Combined active-passive immunisation of horses against tetanus. *Aust Vet J* 1980;56:119–122.
26. Timoney JF. Strangles. *Vet Clin North Am Equine Pract* 1993;9:365–374.
27. Sheoran AS, Sponseller BT, Holmes MA, et al. Serum and mucosal antibody isotype responses to M-like protein (SeM) of *Streptococcus equi* in convalescent and vaccinated horses. *Vet Immunol Immunopathol* 1997;59:239–251.
28. Galan JE, Timoney JF. Mucosal nasopharyngeal immune responses of horses to protein antigens of *Streptococcus equi*. *Infect Immun* 1985;47:623–628.
29. Hoffman AM, Staempfli HR, Prescott JF, et al. Field evaluation of a commercial M-protein vaccine against *Streptococcus equi* infection in foals. *Am J Vet Res* 1991;52:589–592.
30. Rief JS, George JL, Shideler RK. Recent developments in strangles research: observations on the carrier state and evaluation of a new vaccine, in *Proceedings*. 27th Annu Conv Am Assoc Equine Pract 1981;33–40.
31. Staempfli HR, Hoffman AM, Prescott JF, et al. Clinical evaluation of a commercial M-protein vaccine in naturally infected foals, in *Proceedings*. 37th Annu Conv Am Assoc Equine Pract 1991;259–262.
32. Li W, Fiala S, Gigson N, et al. Efficacy of a modified live *Streptococcus equi* vaccine in an equine experimental model, in *Proceedings*. Eighth International Conference on Equine Infectious Diseases 1998;232.
33. Galan JE, Timoney JF, Lengemann FW. Passive transfer of mucosal antibody to *Streptococcus equi* in the foal. *Infect Immun* 1986;54:202–206.
34. Nelson KM, Schram BR, McGregor MW, et al. Local and systemic isotype-specific antibody responses to equine influenza virus infection versus conventional vaccination. *Vaccine* 1998;16:1306–1313.
35. Hannant D, Mumford JA, Jessett DM. Duration of circulating antibody and immunity following infection with equine influenza virus. *Vet Rec* 1988;122:125–128.
36. Mumford JA, Jessett DM, Hannant D. Correlation of antibody to the hemagglutinin with protection against infection with Influenza A/Equine 1 (H7N7) virus. *Proceedings*, Eighth International Conference on Equine Infectious Diseases 1998; 193.
37. Ferguson JA, Reeves WC, Hardy JL. Studies on immunity to alphaviruses in foals. *Am J Vet Res* 1979;40:5–10.
38. Wilson JH, Gibbs PJ, Calisher CH, et al. Investigation of vaccine-induced tolerance to Eastern equine encephalitis virus in foals. *Proceedings*, 41st Annual Conference of the American Association of Equine Practitioners 1995;178–180.
39. Wilson JH, Rubin HL, Lane TJ, et al. A survey of eastern equine encephalomyelitis in Florida horses: prevalence, economic impact, and management practices. *Prev Vet Med* 1986;4:261–271.
40. Green SL, Smith LL, Vernau W, et al. Rabies in horses: 21 cases (1970–1990). *J Am Vet Med Assoc* 1992;200: 1133–1137.
41. Palmer JE, Benson CE, Whitlock RH. Resistance to development of equine ehrlichial colitis in experimentally inoculated horses and ponies. *Am J Vet Res* 1990;51:763–765.
42. Palmer JE. Potomac horse fever. *Vet Clin North Am Equine Pract* 1993;9:399–410.
43. Atwill ER, Mohammed HO. Evaluation of vaccination of horses as a strategy to control equine monocytic ehrlichiosis. *J Am Vet Med Assoc* 1996;208:1290–1294.
44. Dutta SK, Vemulapalli R, Biswas B. Association of deficiency in antibody response to vaccine and heterogeneity of *Ehrlichia risticii* strains with Potomac horse fever vaccine failure in horses. *J Clin Microbiol* 1998;36:506–512.
45. Palmer JE. *Potomac horse fever*. In: Robinson NE, ed. *Current therapy in equine medicine*, vol 3. Philadelphia: WB Saunders, 1992;250–253.
46. Sessions J, Dawson JE. Maryland field evaluation of the Potomac horse fever vaccine. *Equine Pract* 1988;10:7–12.
47. Sessions JE. Potomac Horse Fever studies in Maryland and on an endemic farm, in *Proceedings*. Schering Animal Health sponsored Symposium on Potomac Horse Fever 1987;79–87.
48. Timoney PJ, McCollum WH. Equine viral arteritis. *Vet Clin North Am Equine Pract* 1993;9:295–309.
49. Timoney PJ, McCollum WH, Murphy TW, et al. The carrier state in equine arteritis virus infection in the stallion with specific emphasis on the venereal mode of virus transmission. *J Reprod Fertil Suppl* 1987;35:95–102.