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and mortality rates in neonatal calves, without the use of enteric disease vaccines, by instituting proper sanitation and management practices. Conversely, vaccination programs for neonatal enteric disease are rarely successful in the absence of reasonably good sanitation and management because heavy exposure to causative agents can overwhelm vaccinal resistance and because of problems with cryptosporidiosis, salmonellosis, and other enteric infections for which vaccines are either not available or minimally effective. Vaccination programs are generally unsuccessful when calves are taken from their dams and raised on a milk replacer diet, which does not contain the antibodies that are found in the dam's milk.[11]

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Rotavirus and Coronavirus Vaccines

Bovine rotaviruses and bovine coronavirus cause acute malabsorptive diarrheal disease, primarily in calves less than 3 weeks of age.[1–3] Both agents attack the small intestinal villus enterocytes, causing their wholesale desquamation into the intestinal lumen.[1,4] This is accompanied by a drastic reduction in the numbers and size of small intestinal villi.[1,4] A malabsorption syndrome results from a reduction in surface area for absorption and from a lack of brush border disaccharidase enzymes.[1,4] Affected calves have watery diarrhea and may become hypovolemic, dehydrated, hyponatremic, hypochloremic, acidotic, and hyperkalemic.[1]

General Considerations

Considerable evidence is available to support a conclusion that neither of the two commercial bovine rotavirus-coronavirus vaccine products that are presently available in the United States is capable of providing effective control of bovine rotavirus (BRV) and bovine coronavirus infections in calves, under the constraints prevailing in most commercial cattle production systems. Two approaches have been used in an attempt to protect calves against BRV and coronavirus infections.

The first approach involves *vaccination of neonatal calves with an MLV vaccine* (Calf Guard, Norden Laboratories, Lincoln, NE 68521), *administered by the oral route.* The objective is to stimulate a cell-mediated immune response and local secretory IgM and IgA antibody production by the intestinal mucosa.[5] Calves begin producing detectable levels of local secretory (intestinal) IgM antibodies within 4 to 6 days after successful oral vaccination.[6] This is followed, within 2 to 6 more days, by the appearance of detectable levels of locally produced intestinal IgA antibodies. Calves are resistant to challenge from the initial appearance of local IgM antibodies.[6]

In order to consistently elicit an effective immune response, the vaccine must be administered orally, immediately after birth, and before the calf has nursed. Ordinarily, this is practical only with dairy calves. Because the colostrum of most heifers and cows contains detectable levels of viral neutralizing antibodies,[1,3,4,6-8] administration of colostrum should be delayed for several hours following vaccination, in order to avoid inactivation of vaccine virus. If the calf has nursed before it can be vaccinated, it is recommended that vaccination be delayed until 6 hours after nursing, and that the calf not be fed colostrum again until 6 hours after vaccine is administered.

It has been conclusively shown that Calf Guard is ineffective when a portion of the calves on a farm or ranch are left unvaccinated in double-blind vaccine evaluation studies.[9-11] Apparently, the resistance induced by vaccination is easily overwhelmed by exposure to large amounts of virus shed by unvaccinated calves. However, when all calves were either vaccinated or not vaccinated in sequential comparisons, morbidity and mortality rates from neonatal enteric disease were significantly reduced by vaccination.[9-10] Nonetheless, the design and statistical validity of these latter kinds of trials have been questioned.[12]

Under practical conditions, in the experience of the author and others,[13] this vaccination regimen has seldom resulted in dramatic improvements in calf health. Under commercial conditions, few owners or employees will administer vaccine within minutes after birth or effectively regulate the intake of colostrum in relation to the time of vaccination. Therefore, it is likely that many calves are exposed to infection before they can be vaccinated and that vaccine virus is often neutralized by ingested colostral antibodies.[4,6,14] Consequently, it is likely that relatively few calves are actually immunized under commercial conditions.

The second approach involves *intramuscular vaccination of preg-*

nant cows with either MLV vaccine (Calf Guard, Norden Laboratories) *or an inactivated viral vaccine* (Scourguard 3 [K] Norden Laboratories), in order to ensure that high levels of specific viral neutralizing lactoglobulins will be present in the colostrum and in milk consumed by the calf during the first several days of life. Infectious viral particles are neutralized by these antibodies within the digestive tract of the calf, preventing infection of the intestinal villus enterocytes.[1,8,15,16] Until recently it was believed that circulating passive humoral antibodies, absorbed from the gut of the calf during the first 24 hours of life, did not play an important role in immunity to bovine enteric rotaviral and coronaviral infections.[1,4,7] It is now known, however, that passive humoral BRV antibodies of the IgG_1 class are transferred into the small intestinal lumen, where (in suitable concentrations) they protect against experimental challenge.[16] In addition, vaccination of pregnant cows (at least with an experimental vaccine containing live rotavirus and water-in-oil adjuvant) results in production of antigen-specific transformation colostral lymphocytes. Ingestion of these sensitized colostral lymphocytes by 1-day-old calves confers partial protection against challenge with virulent BRV.[8]

Colostrum, from most vaccinated cows and from some unvaccinated cows, is sufficiently high in virus-neutralizing (VN) antibodies that it is highly protective during the immediate period when it is being consumed by the calf.[1,3,6–8,13,14,16,17] Since most calves become relatively resistant to the adverse clinical effects of BRV and coronavirus infections prior to reaching 3 to 4 weeks of age, these diseases are readily preventable in production systems in which it is feasible to hand-feed colostrum from vaccinated cows throughout the first 3 to 4 weeks of life.[3,18] Even seronegative calves that do not receive colostral BRV antibodies within 24 hours after birth are solidly protected as long as they are fed colostrum or colostrum:milk mixtures that have a minimum BRV VN antibody titer of 1:1024 or higher.[3,8,14,18] Colostrum or colostrum:milk mixtures having BRV VN antibody titers between 1:256 and 1:679 may be partially[3,17–19] or completely protective,[7] depending on (1) the size of the challenge dose of BRV, (2) the virulence of the challenge virus, (3) the degree of antigenic relatedness between the challenge virus and the immunizing virus, (4) the quality of calf management, and (5) the degree of exposure to other enteropathogens.[4,20] Colostrum or colostrum:milk mixtures with BRV VN antibody titers of 1:44 or less are clearly nonprotective.[14,17,18]

The major unresolved problem area, with respect to prevention of BRV and coronavirus infections by vaccination, is the suckling beef calf. Concentrations of BRV and coronavirus VN antibodies in the milk of vaccinated cows fall below protective levels by 3 to 7 days following parturition.[1,2,14,15] Ideally, beef calves from vaccinated dams will develop subclinical enteric viral infections within the first few days after birth, while either milk VN antibody concentrations or (serum-derived) intestinal IgG_1 VN antibody concentrations are still partially protective.[1,4,5,18] However, some calves may not be exposed to BRV and coronavirus until *after* milk antibody concentrations fall below protec-

tive levels. Other calves fail to mount an immune response to viral challenge while protected by lactogenic immunity and remain susceptible to a subsequent exposure.[18,19] Finally, many calves exposed to BRV while protected by lactogenic immunity will begin to shed virus and manifest signs of mild enteric disease within 1 to 9 days after VN antibodies in milk have fallen to nonprotective levels.[18] Unfortunately, in lieu of complete protection, the manifestations of passive immunity to BRV that are often noted are (1) a delay of a few days in the onset of clinical signs,[3,13,17-19] and/or (2) reduced severity of clinical signs,[3,17,18] and/or (3) a reduction in the length of the period of viral shedding associated with infection,[3,8,18] Although there are reports of successful field trials involving BRV/BRV-coronavirus–vaccinated cows,[13,14,17,21-26] negative results[12] have also been reported.

One of the major shortcomings of Calf Guard is its relative inefficiency for boostering serum and colostral antibody titers of seropositive cows.[2-4,12,13,20,27,28] The ranges in BRV VN colostral antibody titers that have been reported in nonvaccinated cows, Calf Guard-vaccinated cows, and Scourguard 3 (K)-vaccinated cows are 1:32 to 1:3200, 1:501 to 1:4395, and 1:2896, respectively (Table 24). Experimental vaccines utilizing live BRV, either in Freund's incomplete adjuvant[27] or in water-in-oil emulsions of mineral oil containing mannide oleate,[8] stimulate much higher BRV VN antibody titers than those obtained with present commercial vaccines (see Table 24). Vaccination with an experimental vaccine of this type resulted in concentrations of BRV VN antibodies in milk of 1:1680 at 30 days after paturition.[27] This is above the levels regarded as being protective.[14] This vaccine was administered by intramuscular injection 8 to 10 weeks before the anticipated calving date and readministered 2 weeks later by infusion into the involuted mammary glands.[27]

At present, there is only one known serotype of bovine coronavirus.[1,5,13] However, at least two serotypes of BRV are known to exist in the United States[29] and Japan,[30] and at least three BRV serotypes exist in Great Britain.[22] Both passive and active immunity to BRV infections are serotype specific.[4,22,31] Some serotypes of human rotavirus (HRV) are pathogenic for calves,[1] and a high prevalence of serum VN antibodies to three different serotypes of HRV has been reported in British cattle.[22]

Both of the bovine rotavirus-coronavirus vaccines that are commercially available in the United States (Calf Guard and Scourguard 3 [K], Norden Laboratories) are prepared utilizing (only) the original Nebraska calf diarrhea rotavirus isolate, which has been designated BRV-1. The implication of this for vaccinal efficacy is, as yet, unclear. Although BRV-1 is thought to be the most common serotype affecting cattle in the United States,[29] some vaccine "breaks" have been found to have resulted from herd infections with heterologous virus.[32] Vaccination with a BRV-1 vaccine of cows seropositive to BRV-1, BRV-2, HRV-1, HRV-2, and HRV-3 resulted in significant increases in serum VN antibody titers to all five agents.[22] This indicates that effective monovalent vaccines could be useful for control of all BRV and HRV serotypes that are present in a herd at the time of booster vaccination.

Table 24. *Effect of Maternal Vaccination with Various Kinds of Bovine Rotavirus Vaccines on Colostral Rotavirus Viral Neutralizing Antibody Titers*

	TYPE OF VACCINE UTILIZED			
NOT VACCINATED	*Commercial MLV*[a,b]	*Experimental MLV*[b]	*Commercial Inactivated*[c]	*Experimental Inactivated*
1:32[d,14e]	1:501[12]	1:204,800[8]	1:2896[2]	1:1024[14]
1:86[2]	1:870[13]	1:360,205[27]		1:1950[35]
1:100[19]	1:2807[20]	1:678,828[18]		1:2560[17]
1:160–1:2560[7]	1:3775[27]			1:2884[35]
1:229[35]	1:4096[4]			1:4467[35]
1:320[17,19]	1:4395[18]			1:4598[4]
1:340[12]				1:13,004[4]
1:512[13]				1:13,004[4]
1:645[24]				1:20,452[19]
1:813[4]				1:32,768[4]
1:1613[20]				
1:2431[27]				
1:2865[18]				
1:200–1:3200[8]				
1:32–1:3200[f]	**1:501–1:4,395**	**1:204,800–1:678,822**	**1:2,869**	**1:1,024–1:32,768**

[a]Calf Guard (Norden Laboratories, Lincoln, NE 68521); [b]MLV = modified-live virus vaccine; [c]Scourguard 3 (K) (Norden Laboratories); [d]BRV VN antibody titer; [e]reference; [f]range of values reported by various investigators.

SCOURGUARD 3 (K) ROTAVIRUS AND CORONAVIRUS VACCINATION PROGRAMS

Scourguard 3 (K) is an inactivated bovine rotavirus-coronavirus vaccine that is combined with an *E. coli* bacterin. General recommendations for use of Scourguard 3 (K) vaccine are summarized (see Table 8). Two doses of vaccine should be administered by intramuscular injection to pregnant cows and heifers at a 2-week interval. The second (immunizing) dose should be given 2 to 3 weeks before the anticipated calving date. Cows that have not calved within 40 days after administration of the immunizing dose should be revaccinated with a single dose. A single annual booster dose should be administered, 2 to 3 weeks prior to each subsequent calving.

This vaccine has a disadvantage in that calves that do not consume adequate quantities of colostrum shortly after birth may not be protected. Newborn calves should be closely observed. Those that do not suckle vigorously within 2 hours after birth should be hand fed or tube fed with 50 to 80 ml/kg body weight of fresh or frozen colostrum.[33,34]

Dairy calves raised on fresh cow's milk are dramatically less susceptible to neonatal enteric disease than those raised on milk replacers (which do not contain lactoglobulins).[13,26,33] Continuous feeding of fresh, frozen, or fermented colostrum from vaccinated cows throughout the first 2 to 4 weeks of life, is a highly effective means of preventing rotaviral and coronaviral infections in dairy calves.[3,7,13,14,18] High-titered colostrum, resulting from vaccination with experimental vaccines, can be preventative when mixed with milk and fed in concentrations as low as 1%.[18] Colostral BRV VN antibody titers achieved with commercial vaccines (see Table 24) should permit successful utilization of colostrum : milk mixtures containing 25 to 50% colostrum.

CALF GUARD ROTAVIRUS AND CORONAVIRUS VACCINATION PROGRAMS

Calf Guard is a MLV rotavirus and coronavirus combination vaccine that is recommended by the manufacturer for administration either to pregnant heifers and cows or to newborn calves but not to both. General recommendations for use of this vaccine in calves and in cows and heifers are summarized (see Table 8).

Calves

Use in calves was previously discussed, under General Considerations.

Cows and Heifers

Two doses of vaccine should be administered by intramuscular injection at a 3- to 6-week interval. The second dose should be administered within 30 days of calving. Cows that do not calve during the first 60 days of the calving season should be given a booster vaccination. An identical regimen is recommended during subsequent pregnancies.

This vaccine does not produce milk and colostral VN antibody titers that are as high and as persistent as those resulting from vaccination with Scourguard 3 (K), mainly because it is relatively ineffective

for boostering humoral and colostral antibody titers of seropositive cows[2-4,12,13,20,27,28]; consequently, it cannot be recommended for this use.

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Escherichia coli *Bacterins*

Enterotoxigenic strains of *E. coli* cause severe diarrheal disease in neonatal calves by colonizing the small intestinal villi, replicating to extremely large numbers (10^9 to 10^{10} *E. coli* per gram of intestinal contents), and producing a heat-stable enterotoxin.[1] *E. coli* enterotoxin causes a net increase in secretion of fluid by small intestinal secretory (crypt) cells, which is the basis for the diarrhea, hypovolemia, dehydration, weakness, shock, hyponatremia, hypochloremia, and acidosis/hyperkalemia that can result.[1–3]

General Considerations

Most *E. coli* bacterins currently marketed in the United States are formulated so as to ensure a high content of K99 pilus (fimbria for