Effects of modified-live bovine viral diarrhea virus vaccines containing either type 1 or types 1 and 2 BVDV on heifers and their offspring after challenge with noncytopathic type 2 BVDV during gestation

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Objective—To compare the efficacy of modified-live virus (MLV) vaccines containing either type 1 bovine viral diarrhea virus (BVDV) or types 1 and 2 BVDV in protecting heifers and their offspring against infection associated with heterologous noncytopathic type 2 BVDV challenge during gestation.

Design—Randomized controlled study.

Animals—160 heifers and their offspring.

Procedures—After inoculation with a placebo vaccine, 1 or 2 doses of an MLV vaccine containing type 1 BVDV, or 1 dose of an MLV vaccine containing both types 1 and 2 BVDV, heifers were bred naturally and challenge exposed with a type 2 BVDV field isolate between 62 and 104 days of gestation. Pregnancies were monitored; after parturition, virus isolation and immunohistochemical analyses of ear-notch specimens were used to determine whether calves were persistently infected. Blood samples were collected at intervals from heifers for serologic evaluation and virus isolation.

Results—Persistent infection was detected in 18 of 19 calves from heifers in the control group and in 6 of 18 calves and 7 of 19 calves from heifers that received 1 or 2 doses of the type 1 BVDV vaccine, respectively. None of the 19 calves from heifers that received the type 1–type 2 BVDV vaccine were persistently infected.

Conclusions and Clinical Relevance—Results suggest that the incidence of persistent BVDV infection among offspring from dams inoculated with 1 dose of the MLV vaccine containing types 1 and 2 BVDV was decreased, compared with 1 or 2 doses of the MLV vaccine containing only type 1 BVDV. (J Am Vet Med Assoc 2006;228:1559–1564)

The prevention and control of BVDV-associated disease centers on the elimination of persistently infected cattle. Identification and removal of persistently infected animals and continued vaccination to prevent fetal infection and subsequent development of persistent infection are the most important components of effective control measures.1 Persistent infections develop following in utero exposure of the fetus (within approx 125 days of gestation) with a noncytopathic strain of BVDV.2 The mechanism of transplacental transfer of BVDV is unknown; however, small amounts of virus in the bloodstream of dams appear sufficient to cause the development of immunotolerant persistently infected calves.3 Protection of the dam may or may not correlate with protection of the fetus from subsequent persistent infection. If viremia of the dam develops, persistent infection of the offspring may develop without apparent clinical signs in the dam.

To break the cycle of in utero and subsequent persistent infections of calves with BVDV, it is essential that vaccination of dams provides fetal protection. Several studies1,4–6 have been conducted to assess the ability of inactivated and MLV vaccines to protect fetuses against either natural or experimental exposure to BVDV. These studies all involved challenge with BVDV strains identified as type 1. Results of further studies4–8 have indicated that monovalent BVDV vaccines containing only a type 1 BVDV strain are capable of conferring a good level of cross-protection against clinical disease caused by type 2 BVDV. One MLV vaccine provided protection against a type 1 BVDV fetal challenge in 10 of 12 calves8; however, use of that same vaccine to protect against a type 2 BVDV challenge resulted in protection of only 8 of 19 calves when birth of persistently infected calves was the measured outcome.9 More recently, modified-live bivalent BVDV vaccines containing types 1 and 2 BVDV strains have been associated with a higher degree of fetal protection against type 2 BVDV than that achieved by use of the aforementioned monovalent type 1 BVDV vaccine10,11; however, the results of bivalent BVDV vaccine administration were not compared with the effects of the same vaccine containing only the type 1 BVDV strain.

The purpose of the study reported here was to evaluate the efficacy of MLV vaccines containing either type 1 BVDV or types 1 and 2 BVDV in protecting heifers and their offspring against infection associated
with heterologous noncytopathic type 2 BVDV challenge during gestation. Protection against development of persistent infection among offspring conferred by administration of 1 and 2 doses of a vaccine containing a monovalent type 1 BVDV fraction to dams prior to viral challenge during gestation was compared with the level of protection provided by a bivalent vaccine that contained the same type 1 BVDV strain and an additional type 2 BVDV strain. Although administration of a booster dose of an MLV BVDV vaccine is not required, it has been hypothesized that multiple doses may act as boosters to increase cross-protection against BVDV fetal infections. The same noncytopathic type 2 challenge strain was used in all experiments.

Materials and Methods

Heifers—All heifers were part of a research herd and were maintained under identical management conditions at a research facility. The second experiment was performed with the newly formulated vaccine comprised of a type 1 BVDV strain and an additional type 2 BVDV strain when unexpected results were obtained in the 2-dose vaccinated group during the first experiment. One hundred sixty nonpregnant beef heifers of breeding age were used. All animals were seronegative (reciprocal serum anti-BVDV antibody titer < 1:2) as determined by type 1 and type 2 BVDV serum neutralization assays. All heifers were also evaluated for BVDV infection via virus isolation from whole-blood samples. None of the heifers had ever received vaccines containing a BVDV faction. All animals were maintained according to current modern ranching practices and current recommendations for cattle care and humane treatment. The study design was reviewed by the site institutional animal care and use committee to ensure humane treatment, and the welfare of all study animals was monitored by attending veterinarians.

Calves—On the day of birth, each calf was identified by a uniquely numbered ear tag. Before ingestion of colostrum (ie, before nursing), a blood sample for virus isolation was collected from each calf. A full-thickness ear-notch tissue sample was also collected from each calf and evaluated for BVDV antigen via immunohistochemistry.

Vaccination of heifers—In the first experiment, 100 heifers were inoculated IM with 2 mL of a placebo vaccine (containing MLV BHV-1, MLV PI3, MLV BRSV, and inactivated bacterins [Campylobacter fetus var fetus and Leptospira interrogans serovars hardjo-bovis, icterohaemorrhagiae, canicola, pomona, and grippotyphosa]) on day 2 (group 5). Forty heifers were each inoculated IM in the neck on day 0 with 2 mL of a combination vaccine containing the same type 1 BVDV strain and an additional type 2 BVDV strain. Although administration of a booster dose of an MLV BVDV vaccine is not required, it has been hypothesized that multiple doses may act as boosters to increase cross-protection against BVDV fetal infections. The same noncytopathic type 2 challenge strain was used in all experiments.

Breeding—Bulls that yielded negative results when evaluated via BVDV isolation were commingled with the heifers 31 days after day 0 in experiment 1 and 56 days after day 0 in experiment 2. Heifers in both experiments were examined for pregnancy via ultrasonography approximately 60 days after exposure to the bulls (ie, day 90 in experiment 1 and day 112 in experiment 2). Twenty heifers from each vaccinated group and 10 heifers from each control group were randomly selected for challenge on the basis of fetal age to minimize the calving interval.

BVDV challenge—The type 2b BVDV strain (94B-5359a) selected for use in the viral challenge was isolated from a persistently infected calf that had been born during an outbreak of BVDV disease in Wyoming. The strain was isolated by the Wyoming Diagnostic Laboratory, plaque-purified, and sequenced. The strain is antigenically heterologous to the type 2 strain in vaccine C. Challenge inocula were prepared from the same frozen stock of challenge virus in both experiments. In experiment 1, heifers were inoculated with a 4-mL dose containing 1 X 10^11 TCID50 of 94B-5359a, whereas in experiment 2, animals were challenged with a 4-mL dose containing 1 X 10^13 TCID50 of 94B-5359a. Two milliliters of challenge virus was instilled into each nostril of all heifers when the fetal age was 75 to 100 days in experiment 1 (ie, on day 125) and 62 to 104 days in experiment 2 (ie, on day 146).

Sample collection—Beginning on day 120 in experiment 1 and day 0 in experiment 2, a general health evaluation of all heifers was conducted at least once weekly. During the 21-day challenge phase of each study and thereafter, a general health evaluation was conducted daily. Multiple blood samples were collected from the dams. Blood was collected on days 0, 14, and 28 in groups 1 and 2; days –120, –106, –92, 0 (which corresponds to the second vaccination), 14, and 28 in group 3; and days 0, 28, 56, and 112 in groups 4 and 5. Blood was also collected on days 125, 146, and 236 after exposure to the viral challenge (ie, on day 125) and 31 days after day 0 in experiment 1 and day 28 in experiment 2; days 125, 146, and 236 after exposure to the viral challenge (ie, on day 146). The fetal age was 75 to 100 days in experiment 1 (ie, on day 125) and 62 to 104 days in experiment 2 (ie, on day 146).

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Conclusion of study—At the conclusion of the study, all heifers were reintroduced into the herd. All nonpersistently infected calves were kept in the herd and raised according to the ranch’s normal procedures. Some of the persistently infected calves were donated to a university to study the long-term impact of persistent infection on calves. The remaining persistently infected calves were euthanized via IV injection of barbiturates.

Statistical analysis—Data were analyzed by use of a mixed-model or categorical procedure. A general linear mixed-model or categorical procedure was used to analyze rectal temperature and serum antibody titers. A Fisher exact test was used to compare the proportion of dams that yielded positive results via virus isolation, the proportion of persistently infected calves, and the number of days that virus was isolated from each heifer that had at least 1 positive virus isolation result following viral challenge. A value of $P \leq 0.05$ was considered significant. Descriptive statistics were calculated as appropriate.

Results

Prechallenge findings—All heifers were seronegative (reciprocal serum anti-BVDV antibody titer < 1:2) for both types 1 and 2 BVDV-neutralizing antibodies on day 0, and control cattle remained seronegative until challenged with the virulent type 2 BVDV strain. All cattle also yielded negative results via BVDV isolation at the initiation of the study and on the day of challenge. None of the heifers that received vaccine treatment subsequently developed lethargy or injection-site swellings.

Clinical observation—During the 21-day observation period following viral challenge, no clinical signs attributable to BVDV exposure and no consistent increases in rectal temperature (compared with prechallenge examination findings) were detected in any heifers in any study group. Although some significant differences in mean rectal temperatures among groups were detected, values remained within the reference range (Table 1).

Serologic evaluations—Serologic responses against type 1 BVDV were detected in all heifers that received BVDV vaccine by 28 days after treatment (Table 2). Heifers in treatment group 3 received 2 doses of vaccine; the response following the second dose of vaccine on day 0 was more rapid and greater than that detected in heifers in groups 2 and 5 that received their primary dose, indicating that an anamnestic response was elicited in group 3. However, by the day of viral challenge, there were only slight differences in serum titers of antibodies against type 1 BVDV among groups that received BVDV-vaccine treatment. Compared with prechallenge serum antibody titers, titers against type 1 BVDV in the placebo control heifers in groups 1 and 4 were marginally increased after viral challenge, whereas titers substantially increased in all 3 groups that received BVDV-vaccine treatment.

Serologic responses against type 2 BVDV were also detected in all heifers that received BVDV-vaccine treatment (groups 2, 3, and 5) by 28 days after vaccination.
(Table 3); however, by the time of viral challenge, serum antibody titers of heifers treated with the type 1-type 2 BVDV vaccine (group 5) were substantially higher than the titers of heifers in either of the groups receiving 1 (group 2) or 2 (group 3) doses of the monovalent type 1 BVDV vaccine. All BVDV-vaccine–treated groups had substantially higher prechallenge serum antibody titers than the control groups, which remained seronegative. Both placebo control groups seroconverted after challenge exposure, and serum anti-BVDV antibody titers were increased markedly by 111 days after challenge in experiment 1 (group 1) and 132 days after challenge in experiment 2 (group 4), suggesting constant stimulation of the dams’ immune systems because of persistent infection of the fetuses. This progressive increase in serum antibody titer was not detected in the BVDV-vaccine–treated groups.

**Virus isolation**—Nine of 10 placebo control heifers in group 1 (experiment 1) yielded positive results via virus isolation on at least 1 of the sampling days after challenge (Table 4). On days 4, 6, 8, 10, and 14 after viral challenge, viremia was detected in 2, 5, 7, 7, and 2 of the placebo control heifers, respectively, whereas virus was only isolated from 1 of the 20 heifers in each of the BVDV-vaccine–treated groups (groups 2 and 3). In experiment 2, all 10 placebo control heifers (group 4) were viremic on at least 1 of the sampling days after viral challenge. On days 6 through 10 after viral challenge, viremia was detected in 12, 18, 18, 16, and 10 of the placebo control heifers, respectively, whereas BVDV was not isolated from any of the heifers (0/20) in the group receiving the type 1-type 2 BVDV vaccine (group 5) on any of the sampling days after viral challenge, which represented a significant ($P \leq 0.05$) difference.

**Offspring**—Eighty heifers were pregnant on the day of viral challenge. Following a normal gestation period, 74 heifers each gave birth to a single calf. Six heifers were excluded from the study because of fetal loss (Table 5).

**Persistent infection among calves**—Virus isolation and immunohistochemical analysis of samples (blood and ear-notch tissue specimens, respectively) collected after birth from calves of placebo control heifers (groups 1 and 4) revealed that a high number of calves were persistently infected with type 2 BVDV (Table 5). Isolated viruses were identified by type and sequenced to identify the strain causing the persistent infection. The strain was identified as the challenge strain. Of the calves born to placebo control heifers, 9 of 10 were persistently infected in experiment 1, and 9 of 9 were persistently infected in experiment 2.Significantly ($P \leq 0.05$) fewer persistently infected calves were identified in each of the BVDV-vaccine–treated groups (groups 2, 3, and 5). However, protection in the groups that received the monovalent BVDV vaccine was considered incomplete because 6 of 18 calves from heifers that received a single dose of type 1 BVDV vaccine (group 2) were persistently infected, as were 7 of 19 calves from heifers that received 2 doses of the same monovalent BVDV vaccine (group 3). No significant ($P > 0.05$) differences were detected between the number of persistently infected calves born to heifers treated with a single dose or double dose of the type 1 BVDV vaccine. In contrast, administration of the bivalent MLV BVDV vaccine to heifers prior to breeding appeared to provide complete protection of fetuses against the development of persistent infection after viral challenge during gestation because none of the calves from heifers treated with type 1-type 2 BVDV vaccine (group 5) were persistently infected.

**Table 3**—Geometric mean serum neutralizing antibody titers* against type 2 BVDV following challenge with heterologous noncytopathic type 2 BVDV during gestation in heifers treated prior to breeding with MLV vaccines containing either type 1 BVDV or types 1 and 2 BVDV or placebo vaccine.

<table>
<thead>
<tr>
<th>Treatment group (No.)</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>14</th>
</tr>
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<tr>
<td>1 (20)</td>
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<td>NA</td>
<td>NA</td>
<td>1.0</td>
<td>1.0</td>
<td>1.3</td>
<td>6.6</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2 (40)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.0</td>
<td>1.6</td>
<td>22.8</td>
<td>38.9</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3 (20)</td>
<td>1.0</td>
<td>1.2</td>
<td>NA</td>
<td>16.0</td>
<td>22.8</td>
<td>38.9</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>4 (20)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.0</td>
<td>NA</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>5 (40)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.0</td>
<td>NA</td>
<td>57.2</td>
<td>532.3</td>
<td>496.8</td>
<td>332.0</td>
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</tbody>
</table>

See Tables 1 and 2 for key.

**Table 4**—Number of heifers (treated prior to breeding with MLV vaccines containing either type 1 BVDV or types 1 and 2 BVDV or placebo vaccine) with viremia following challenge with heterologous noncytopathic type 2 BVDV during gestation.

<table>
<thead>
<tr>
<th>Treatment group (No.)</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
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<th>8</th>
<th>9</th>
<th>10</th>
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<td>7</td>
<td>NA</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>2 (20)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>1</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3 (20)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4 (10)</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
<td>9</td>
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<td>8</td>
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<td>NA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

Fetal age (estimated ultrasonographically) ranged from approximately 75 to 100 days in groups 1 through 3 and 62 to 104 days in groups 4 and 5.

*Values with different superscript letters are significantly ($P \leq 0.05$) different.

See Table 1 for key.
Table 5—Number of calves with persistent infection from heifers treated prior to breeding with MLV vaccines containing either type 1 BVDV or types 1 and 2 BVDV or placebo vaccine and challenged with heterologous noncytopathic type 2 BVDV during gestation.

<table>
<thead>
<tr>
<th>Treatment group (No. of heifers)</th>
<th>No. of calves with persistent BVDV infection</th>
<th>No. of calves yielding positive results via virus isolation</th>
<th>No. of calves yielding positive results via immunohistochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (10)</td>
<td>9/10</td>
<td>7/10</td>
<td>8/10</td>
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<td>6/18</td>
<td>4/18</td>
<td>6/18</td>
</tr>
<tr>
<td>3† (20)</td>
<td>7/19</td>
<td>7/19</td>
<td>7/19</td>
</tr>
<tr>
<td>4‡ (10)</td>
<td>9/9</td>
<td>7/9</td>
<td>9/9</td>
</tr>
<tr>
<td>5 (20)</td>
<td>0/18</td>
<td>0/18</td>
<td>0/18</td>
</tr>
</tbody>
</table>

*Only 18 calves were available for data collection because of fetal loss following viral challenge. †Only 19 calves were available for data collection because of fetal loss following viral challenge. ‡One heifer was no longer pregnant at 56 days after challenge; the fetus was severely decomposed, and the cause of the abortion was undetermined. §One heifer was no longer pregnant 132 days after challenge, and another heifer aborted 137 days after challenge. No causes for the abortions were determined, and BVDV was not identified via virus isolation of lung, kidney, or spleen specimens or via immunohistochemical staining of thymus, spleen, ear, or ear-notch tissue samples.

See Table 4 for remainder of key.

Discussion

In recent years, the focus of efficacy studies to evaluate BVDV vaccines has shifted from the prevention of clinical disease to the prevention of fetal infection and birth of persistently infected calves. The ability of various vaccines to prevent the birth of calves with persistent infection caused by type 1 BVDV strains has been widely investigated. Although cross-protection provided by type 1 modified-live BVDV vaccines against clinical disease caused by type 2 BVDV challenge has been well documented,9–14 the prevention of fetal infection and persistent infection of calves by such cross-protection was considered incomplete. The type 1 BVDV (NDL) vaccine strain used in one of those previous studies14 was the same type 1 strain used in the present study. In 2 other studies15,16 in which bivalent BVDV vaccines were used, a higher level of fetal protection against development of persistent BVDV infection was provided, compared with that achieved via treatment with monovalent vaccine; however, it was not determined whether the protection was attributable to the inclusion of a type 2 BVDV strain, the inclusion of BVDV strains that were different from those used in previous studies, or the increased BVDV content of the vaccine. Additionally, it had been hypothesized that a booster dose of a monovalent type 1 BVDV vaccine would improve the level of fetal cross-protection after challenge with type 2 BVDV. Results of the present study indicated that multiple vaccinations with a type 1 MLV BVDV vaccine did not improve fetal protection against type 2 BVDV infection and that the inclusion of the type 2 MLV BVDV component increased the level of fetal protection even against a higher dose of the same challenge virus.

The means by which vaccination of a dam provides fetal protection is not yet known, although it has been suggested that preventing viremia in the dam is the principal mechanism through which control of BVDV infection in a fetus is provided. Currently, it is not known whether the complete absence of viremia in the dam is necessary for fetal protection; decreased levels of viremia or decreased duration of viremia following infection in vaccinated calf (compared with the course of infection in unvaccinated calf) may have an effect on the development of persistent infection in calves. The results of the present study also indicated that virus isolation following exposure cannot be used as the sole indicator of fetal infection because viremia was not detected after BVDV challenge in most of the heifers treated with the type 1 BVDV vaccine (groups 2 and 3). However, approximately one third of these heifers gave birth to persistently infected calves. Viremia may have developed on days when samples were not collected from the heifers, may have developed to levels that were undetectable via virus isolation methods, or may have developed for a short period and was undetected. As vaccination programs for BVDV control are designed, the differences in fetal protection provided by various vaccines must be taken into consideration. Vaccines that have proven fetal protection against both type 1 and type 2 BVDV should be chosen. The data obtained in the present study suggest that protection against development of persistent BVDV infection in calves in utero will be considerably improved if the vaccine administered to dams before breeding contains both type 1 and type 2 BVDV.

References


