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# Neonatal Immune Development in the Calf and Its Impact on Vaccine Response

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Probably no area of calf management is filled with more questions than the development of an effective vaccine program. In assembling this article, it is clear that many “vaccine recommendations” have been made but little research is available to indicate the true effectiveness of vaccine timing or ideal protocols for use in young calves. The development of the immune system in calves progresses, in small steps, from conception to maturity at approximately 6 months after birth (Fig. 1). Neonatal and young calves depend on passive immunity transferred from cows as the primary basis for protection against disease. Antibody from cows, transferred with colostrum, activates and regulates the innate responses present in calves to fight infection. This passive immunity is a double-edged sword for young calves: protection from disease on one hand versus interference with a calf’s ability to develop immunity to vaccine antigen. In this article we cover the immunologic response as it develops, the components of passive immunity, and the immune response of young calves. We discuss interference from maternal immunity in the development of specific immunity and vaccine strategies for developing protection against pathogens in calves.

## Immunologic development in utero

An excellent review of the immunologic development of the bovine fetus was recently published [1]. Fetal calves are predominately protected by the

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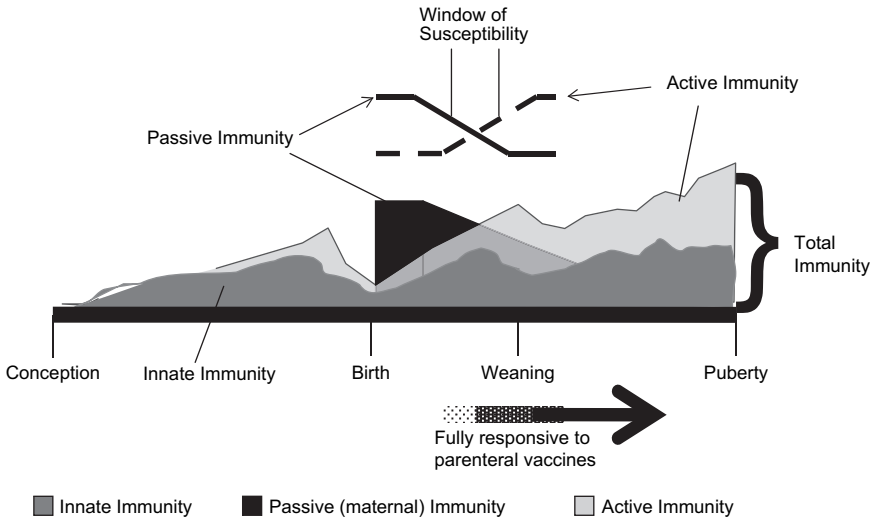


Fig. 1. Development of the immune response in the calf: from conception to puberty. (Data from Morein B, Abusugra I, Blomqvist G. Immunity in neonates. *Vet Immunol Immunopath* 2002;87:207–13; and Butler JE, Sinkora M, Wertz N, et al. Development of the neonatal B and T cell repertoire in swine: implications for comparative and veterinary immunology. *Vet Res* 2006;37:419.)

innate immune system (Fig. 1). The innate immune response mediated by phagocytic cells (neutrophils and macrophages) does not fully develop until late gestation, and there is decline in functional capacity as gestation approaches because of the increase in fetal cortisol levels [1]. Humoral elements, such as complement, are present; however, their levels are below those of adults. Interferon can be induced in a fetus as early as 60 days of gestation [2]. All of the cellular components of the acquired immune response are present in fetal calves [3]. The number of peripheral blood T cells dramatically decreases beginning 1 month before birth as they traffic and populate lymphoid tissues of fetal calves (decrease from approximately 60% to 30% at birth). B cells are present in much lower numbers in developing fetuses (1%–2%) than mature calves (10%–20%) [4,5]. A hallmark of bovine fetuses is agammaglobulinemia [1]. They have almost no antibodies unless infected in utero; even then, they have relatively low levels compared with adults and it is comprised predominantly of IgM [1].

The immunologic response of a fetus to antigens and pathogens increases with the stage of fetal development. In the case of bovine viral diarrhoea virus (BVDV) infection, fetuses infected with BVDV between 45 and 175 days of gestation can lead to immunologic tolerance, and the calves become persistently infected with BVDV. Persistently infected calves never mount a protective response to this infection [6]. Fetal lymphocytes are responsive to mitogens by 188 to 253 days of gestation [7]. By 120 days, fetuses can develop antibodies to parainfluenza virus-3 and to BVDV by 190 days [8].

Although fetuses can respond immunologically to these pathogens, congenital infections with BVDV (eg, in the last half to one third of gestation) can result in negative health and reproductive consequences on young calves and heifers [9,10]. These effects include a twofold increase in severe illness (diarrhea or pneumonia) in young calves [9] and up to a 1.5-month delay in the onset of estrus [10]. Because there is no accurate method for assessing immunologic or reproductive damage from congenital BVDV infections, one should exercise caution when considering retaining “normal” heifers born in a herd that exhibits clinical problems resulting from BVDV reproductive disease (ie, abortions, persistent infections, weak calves).

### *Passive immunity*

Newborn calves are immunologically naïve at birth. They have had no chance to enhance adaptive immunity by “experience” because of the protective environment in the womb, which also limits the activation of phagocytes and their entry into the tissues. Calves are further handicapped by maternal factors and the hormonal influences of parturition and by their lack of antibodies in circulation and in the tissues. The ingestion of colostrum is essential for providing neonates with immunologic protection during at least the first 2 to 4 weeks of life (Fig. 1).

### *Colostrum*

Colostrum is composed primarily of antibodies, cytokines, and cells. Antibody is a critical component of colostrum and provides an immediate source of antibody for agammaglobulinemic calves. Calves that ingest colostrum shortly after birth have significant concentrations of immunoglobulin in serum, whereas colostrum-deprived calves have only trace amounts of immunoglobulin during the first 3 days of life [11]. Endogenous production of IgM in colostrum-deprived calves does not begin to appear in the circulation until 4 days after birth and does not reach functional levels (1 mg/mL) until 8 days of age. Levels of circulating IgA, IgG<sub>1</sub>, and IgG<sub>2</sub> do not reach appreciable levels in these calves until 16 to 32 days after birth [12]. The levels of these antibodies do not approach adult levels until approximately 4 months after birth; at that time IgG<sub>2</sub> is only half of adult levels, which indicates a strong T-helper 2 cell (TH2) bias [12].

The second family of components of colostrum includes cytokines [13]. These immunologic hormones help in the development of the fetal immune response. It is not clear if these cytokines are secreted in the mammary gland, produced by the leukocytes found in colostrum or both. Interleukin 1-beta (IL-1beta), IL-6, tumor necrosis factor-beta, and interferon-gamma are present in bovine colostrum and are associated with a proinflammatory response and may help in the recruitment of neonatal lymphocytes into the gut to aid in normal immune development. Colostrum rapidly improves the ability of neutrophils to phagocytize bacteria, which is primarily accomplished by

absorption of small molecules such as cytokines [14]. Work in pigs has demonstrated that colostral cytokines are absorbed and can be detected in the blood [15]. The level of these cytokines (IL-4 > IL-6 > interferon-gamma > IL-10) peaked at 1 to 2 days postpartum. The high levels of two anti-inflammatory cytokines, IL-4 and transforming growth factor beta-1, suppress local secretion of proinflammatory cytokines in the intestine and allow gut microbial colonization.

The third family of components of colostrum includes cells. Colostrum contains between  $1 \times 10^6$  and  $3 \times 10^6$  cells/mL—almost exclusively leukocytes [16]. These viable leukocytes are present in percentages similar to peripheral blood, but with a larger fraction of macrophages (40%–50%) and a smaller fraction of lymphocytes (22%–25%) and neutrophils (25%–37%) [17,18]. Most lymphocytes are T lymphocytes, with less than 5% being B lymphocytes. Some of these maternal cells enter the circulation and reach peak levels 24 hours after birth [19]. Animals that receive colostrum that contains maternal leukocytes develop antigen-presenting cells faster [18]. This is important because antigen-presenting cells are the keystone cell for development of an acquired immune response to pathogens or vaccines. Pathogen-specific maternal T lymphocytes from vaccinated cows have been isolated from neonatal calves with maximum inducible proliferation at 1 day after birth [20]. The exact role of these cells in the long-term development of pathogen-specific acquired immunity is not clear because they are no longer detectable in the circulation at 7 days of age.

#### *Intake and absorption of the colostrum by neonates*

In normal, full-term neonatal calves, colostral absorption is accomplished through intestinal cells by the neonatal receptor FcRn and endocytosis using “transport vacuoles” [21,22]. This absorptive capacity begins to decrease 6 to 12 hours after birth and ends by 48 hours [21,23]. Neonatal corticosteroid levels must be high to increase colostral absorption [23]. Cold stress, premature birth, cesarean section, and dystocias inhibit neonatal cortisol release and decrease colostral absorption. The administration of corticosteroids to premature newborn calves may enhance their survival [24].

#### *Active immunity in calves*

Although all essential immune components are present in neonates at birth, many of the components are not functional until calves are at least 2 to 4 weeks of age and may continue to develop until puberty [19]. Developing and newborn calves are subject to several immunomodulatory effects (Fig. 2). The placenta produces progesterone, prostaglandin E<sub>2</sub>, and cytokines (eg, IL-4 and IL-10) that affect the near-term fetus and the dam and suppress cell-mediated and memory (TH1) responses. In contrast, these mediators promote TH2 responses and antibody production [25]. Cows also produce estrogen and cortisol before parturition that have immunosuppressive effects

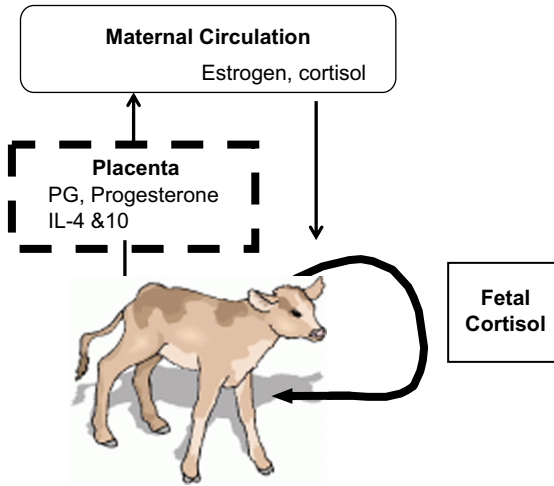


Fig. 2. Immunosuppression of the neonatal calf. (Adapted from Morein B, Abusugra I, Blomqvist G. Immunity in neonates. *Vet Immunol Immunopath* 2002;87:207–13; with permission. Calf clipart from [www.clipartheaven.com](http://www.clipartheaven.com).)

[26]. Finally, as part of the parturition process calves produce high levels of cortisol that remain elevated for the first week of life [27]. The cumulative effect of these hormones is to suppress immune responses and direct the immune response away from the TH1 response. These hormones also promote short-term TH2 immune responses, particularly production of IgM (Box 1).

### Box 1. Immune status of the neonatal calf

#### *Decreased native defense mechanisms*

- ↓ Complement activity
- ↓ Neutrophil and macrophage activity
- ↓ Interferon production
- ↓ Natural killer cell function
- ↓ Dendritic cells

#### *Decreased acquired immune mechanisms*

- Decreased lymphocyte responsiveness
- Neonates have TH2 response: antibody, no memory
- ↓ Major histocompatibility complex II: ↓ antigen presented to T cells
- Born with no memory T or B cells
- Antibody production ↓ CD40 ↓ CD40L B-cell differentiation
- Agammaglobulinemic: must obtain antibody from the mother through colostrum

### *Innate immunity*

The humoral components of the innate system are present in limited quantity and do not function as well as in adults (**Box 1**). Complement activity in newborn calves at birth is approximately 50% of that in adult cows. The circulating complement is quickly diminished to less than 20% of the level circulating in adult cows at 1 day of age. The levels of complement in circulation gradually increase and by 1 month of age have risen to approximately 50% of the level in adults [28]. Interferon activity in the epithelial cells of neonates appears normal, but the production of type 1 interferon by leukocytes is lower [28]. The cellular components of innate immunity are also affected: the number of neutrophils circulating in the newborn calf is approximately four times higher than in 3-week-old calves. Neonatal neutrophils and macrophages have reduced phagocytic ability, but their capacity is increased after the ingestion of colostrum [14]. By 1 week of age, neutrophils are functional and able to mount an effective response [4]. Neutrophil function gradually improves to adult levels by 5 months of age [29]. The number of dendritic cells is lower in neonates, and their ability to present antigen to activate the acquired immune system is limited [25]. Monocytes migrate to the tissues and develop into dendritic cells after proinflammatory stimulation. The number of circulating natural killer cells is also lower at 1 week of age (3% of total lymphocytes) than in adults. The fraction of circulating natural killer cells increases to 10% by 6 to 8 weeks of age [4].

### *Acquired immunity*

The neonatal calf is agammaglobulinemic and depends on colostrum intake for immunoglobulins. The number of circulating B cells is greatly reduced in the neonate, representing only 4% of the total lymphocytes at 1 week of age compared with approximately 20% to 30% in adults. The fraction of B cells in circulation increases gradually to 20% of total lymphocytes by 6 to 8 weeks of age [4]. This low number of B cells coupled with the calves' endogenous corticosteroids and absorbed maternal hormones results in a prolonged lack of endogenous antibody response, even in the face of an apparent TH2 cytokine bias in neonates [30]. Endogenous production of IgM in colostrum-deprived calves does not begin to appear in circulation until 4 days after birth and does not reach expected functional levels (1 mg/mL) until 8 days of age. Levels of circulating IgA, IgG<sub>1</sub>, and IgG<sub>2</sub> do not reach appreciable levels until 16 to 32 days after birth [12].

T-cell subsets have an adult-like ratio (CD4:CD8) in neonates [3,4]. CD3-positive T cells represent 28% to 34% of total lymphocytes with CD4 helper cells at approximately 20% and CD8 cytotoxic T cells at approximately 10% [4]. Gamma-delta T cells represent approximately 25% of the total lymphocytes during the first week but decrease to approximately 16% by 19 to 21 weeks of age. The total number of gamma-delta cells in circulation does not change, but their fraction of circulating lymphocytes decreases as the percentage of B cells increase and the total numbers of T cells increase

[4]. Mitogen activation of T lymphocytes is slightly depressed at birth and remains constant through 28 days after birth [30].

### *Maternal interference and active immunity*

Certainly one of the major challenges in developing an active immune response in young calves has been interference from maternal immunity (see Fig. 1) [25]. This problem has been demonstrated with several pathogens, including rotavirus [31], BVDV [32], bovine respiratory syncytial virus (BRSV) [33,34], bovine herpesvirus-1 (BHV-1) [35], and *Mannheimia (Pasteurella) haemolytica* [36]. The timing of many vaccines administered by the parenteral route involves estimating when the level of maternal antibody is low enough for an active immune response to progress sufficiently to provide vaccine immunity (see Fig. 1). Most maternal antibody has a decay half-life of 16 to 28 days [37]. The prime window for vaccination can be anywhere from a few weeks to 8 months. As illustrated in Fig. 1, this period can vary by animal and depends on the level of maternal antibody and the vaccine antigen, which presents a major challenge for vaccine development. Antibody levels often decay to a level still high enough to block responses to vaccine but not high enough to resist a field infection, which creates a window of opportunity for infecting organisms.

For viruses such as BHV-1 and BVDV, 3 to 4 months of age is often a good time to administer modified live vaccines (MLV). Parenteral vaccination, at 10 days of age with a four-way viral MLV followed by a booster at 6 months of age, did not result in an anamnestic antibody response against either BRSV or BHV-1 [38]. Parenteral vaccination with either inactivated or MLV at 7 weeks of age in the presence of maternal antibodies resulted in a cellular response for the MLV group with no increase in antibody titers for either vaccine. Revaccination with either vaccine 4.5 months later resulted in an anamnestic response in antibody titers [39], which indicated the importance of timing. For bacterins, the period of maternal antibody interference is usually shorter; for example, 40% of colostrum-fed calves vaccinated with *M haemolytica* seroconvert at 2 and 4 weeks of age [36].

Developing protective, active BRSV immunity is one of the more difficult issues in calves. It has been observed that maternal interference is often present in 1- to 6-month-old calves. Developing a vaccination plan to avoid the “window of susceptibility” to BRSV infection is an important but difficult goal (see Fig. 1). The problem with BRSV is that antibody decay is long—approximately 40 days—and that titers as low as 1:4 can interfere with MLV BRSV parenteral vaccines [40].

Approaches using vaccines have been developed to overcome maternal interference. One of the most successful strategies against maternal antibody interference is the use of intranasal (IN) vaccines for BHV-1 [41,42], BRSV [36,43], and PI3 [41,42,44] in young calves. Additional experimental studies with IN BVDV in 2- to 5-week-old calves also provided protection against



BVDV challenge [39,45]. An experimental IN live *Pasturella multocida* vaccine also has been developed and has been shown to induce high levels of secretory antibody [42]. IN vaccines have the advantage of being able to replicate in the nasal mucosa and prime the mucosal immune system with little interference from secretory antibodies. The mucosal immunity primed by IN vaccines is also more likely to prevent infection rather than just reduce disease. Low or no systemic antibody titers often are detected after IN vaccination, which makes it difficult to assess immunity using serology [43]. Despite the lack of “seroconversion,” IN vaccines have generated protective immunity that lasts for months [34,41,45]. An additional advantage of IN vaccines is their ability to induce interferon to induce the antiviral state within 40 hours after administration. Induction of interferon in young calves also may aid in the development of a mature immune system.

Another approach to overcoming maternal immunity is the use of adjuvanted parenteral vaccines [25]. Although it is clear that adjuvanted vaccines can overcome maternal interference, only three reports of their successful use in young calves are available. An adjuvanted inactivated commercial viral vaccine used in 4- to 5-week-old calves protected them against a BRSV challenge at 7 to 8 weeks of age [46]. An adjuvanted viral MLV used in 5-week-old seropositive calves protected against a virulent BVDV challenge at 5 months of age [47]. An inactivated viral vaccine given to 7-week-old calves primed animals who, when revaccinated 14 weeks later, developed a memory BVDV antibody response [39].

### **Increasing memory response by breaking the TH2 bias**

Experiments performed in mice have demonstrated that potent adjuvants can break the TH2 bias in 2-day-old mice. Sendai virus vaccines adjuvanted with immune-stimulating complexes stimulated a TH1 immune response prominent in interferon-gamma, whereas a Sendai virus vaccine adjuvanted with the traditional Al(OH)<sub>3</sub> adjuvant produced a TH2 response [25]. Of particular note in these experiments, only the TH2-biased adjuvant, Al(OH)<sub>3</sub>, was capable of producing significant antibody levels, which were confined to the non-memory TH2 IgG1 subclass [25].

To date, two experimental vaccine systems have demonstrated the ability to break the TH2 bias in young livestock. Small DNA sequences, called oligodeoxynucleotides, containing one or more unmethylated CpG motif (CpG ODN) have been shown to be potent stimulators of TH1 immune responses when used as vaccine adjuvants. One-day-old piglets vaccinated with attenuated pseudorabies virus with an adjuvant system containing CpG ODN induced significant cellular proliferation and interferon-gamma production in response to vaccine antigen within the first week after vaccination [48]. This vaccine also induced significant antibody titers. An even better TH1 immune response was obtained by adding a plasmid expressing the proinflammatory TH1-inducing porcine IL-6 to CpG ODN adjuvanted PRV vaccine [49].

Neonatal calves vaccinated subcutaneously 8 hours after birth with attenuated *Mycobacterium bovis* bacillus Calmette-Guerin developed effective TH1-biased immunity [50,51]. These calves demonstrated strong antigen-specific interferon-gamma and IL-2 responses to *M bovis* purified protein derivative. Upon challenge with virulent *M bovis* at 14 to 17 weeks of age, 100% of calves vaccinated with bacillus Calmette-Guerin were protected from development of tuberculous lesions, whereas all (10/10) unvaccinated controls developed lesions. It was noted in these experiments that none of the calves developed significant levels of *M bovis*-specific antibody [51]. One-week-old calves vaccinated with bacillus Calmette-Guerin also generated significant cell mediated immunity but failed to produce significant antibody responses; conversely, young adults effectively produced cell-mediated immune responses and serum antibody titers [52]. The take-home message is that cell-mediated responses to vaccines can be induced early; however, animals may need to be as old as 3 to 4 weeks before vaccines induce corresponding antibody responses that develop 10 to 14 days after vaccination.

### **Frequency of vaccination and interval between vaccinations: can we overvaccinate?**

Many vaccine protocols have been developed to vaccinate young calves at frequencies as often as weekly during the first and second months of age. Finding any experimental studies that support this frequency is difficult. From other immune systems, it is clear that too frequent vaccination in young animals can lead to antigen-specific tolerance (ie, the lack of any immune response to the antigen) [53], which is the result of suppressive T cells and the deletion of T and B clones specific for those antigens. Another possible adverse outcome of overvaccination is autoimmunity, whose development is based on priming against the animal's own antigens (self) or closely mimicking vaccine antigens to the animal's own antigens. An example of this mimicry is antibodies against one of the surface proteins of infectious bovine rhinotracheitis (IBR) cross-reacting with a surface protein of the immune cells [54]. Stimulation of inflammatory mechanisms associated with vaccination (eg, adjuvants such as alum or microbial ligands) or repeated re-exposure to vaccine components that drive expansion of autoimmune B- and T-cell clones may occur with frequently repeated vaccine stimulation [55,56]. In all animals after vaccination there is expansion in the populations of responding T- and B-cell clones (Fig. 3). Requirements for good immune response are that this clonal expansion stops and that an active process of cell death (apoptosis) occurs (see Fig. 3). This "waning process" allows "culling" of T or B cells that may be poor responders or even cause autoimmunity to be removed by apoptosis [57]. This whole process from vaccination to achieving homeostasis takes at least 3 weeks for the development of a primary response, which can then be boosted to get a true anamnestic secondary response.

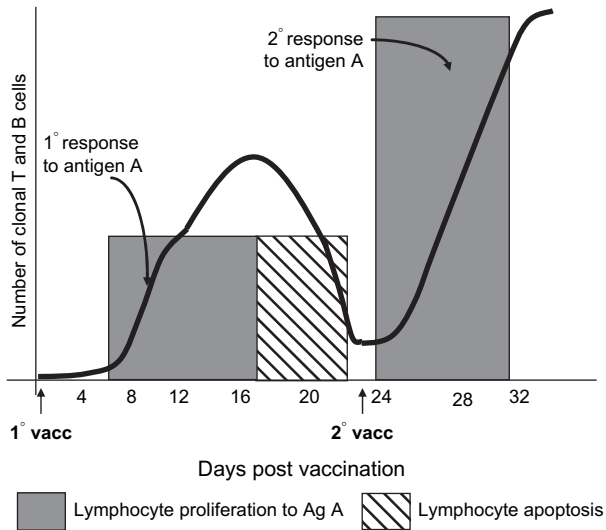


Fig. 3. Importance of vaccine timing and the booster response. (Courtesy of D. Topham, PhD, Rochester, NY.)

### Developing a vaccination program

The first necessity of planning a calf vaccine program is to assess the disease risks at the production site. Often “blanket vaccination” programs are suggested for many pathogens, which may or may not be a threat to young calf health. One must carefully review the antigens that are being used to make sure that they make sense for the operation. Second, the effect of maternal immunity and the age of the calf must be considered. The relationship is linear: the younger the calf, the poorer the response; the older the calf, the better the response. The inverse relationship is true from the standpoint of protection afforded by maternal immunity: the younger the calf, the better the protection because of high levels of maternal antibody; the older the calf, the more susceptible to disease because of waning maternal antibody.

Management factors also come into play. In dairy operations, isolation of calves from exposure to pathogens and good biosecurity can provide a window of enhanced protection by maternal immunity giving an extended window before vaccination is necessary. Some practices, such as feeding waste milk on dairies, may “break” the isolation by introducing pathogens and antibiotics that alter the natural flora developing in the calf to make them more susceptible. This may warrant a more aggressive vaccination program.

#### *Bovine respiratory syncytial virus vaccines*

Active immunization for BRSV is probably the most difficult because of maternal interference (Table 1). It requires careful monitoring and frequent revaccination so that calves can be protected before they reach the “window

Table 1  
Vaccine strategies in colostrum-fed calves: pathogens, route, and timing

| Pathogen                                | Delivery (IM, IN, SC)    | Formulation (MLV or inactivated) | Youngest age to mount a protective response                          | Epidemiologic consequence           | Disadvantages/problems                      |
|---|--------------------------|----------------------------------|--|-------------------------------------|---|
| BRSV                                    | IM, IN <sup>a</sup> , SC | MLV, inactivated                 | IN-MLV, 2 wk [43],<br>3 wk [34], IM-inactivated<br>4–5 wk [46]       | important pathogen<br>< 4 mo of age | highly susceptible to antibody interference |
| BVDV                                    | IM, SC                   | MLV, inactivated                 | IM-adjuvanted<br>MLV 5 wk [47]<br>IM-MLV or<br>inactivated 7 wk [39] | important pathogen<br>> 4 mo of age | MLV immunosuppression                       |
| BHV-1 (IBR)                             | IM, IN, SC               | MLV, inactivated                 | IN-MLV, 2 d [41]   | important pathogen<br>>4 mo of age  | MLV immunosuppression, lifelong latency     |
| <i>Clostridial</i> spp                  | SC                       | inactivated, toxoid              | SC-inactivated,<br>toxoid 170 d [58]                                 | important pathogen<br>0–9 mo        | local reactions                             |
| <i>Mannheimia</i><br><i>Pasteurella</i> | SC                       | MLV, inactivated,<br>toxoid      | inactivated-toxoid<br>6 wk [36]                                      | important pathogen<br>0–9 mo        |   |
| <i>Mycoplasma</i><br><i>bovis</i>       | SC                       | inactivated                      | ND   | important pathogen<br>0–9 mo        |   |
| <i>Salmonella</i> spp                   | SC, IM                   | MLV, inactivated,<br>subunit     | SC-MLV 2 wk  | important pathogen<br>0–9 mo        | MLV immunosuppression                       |
| Rotavirus,<br>Coronavirus               | oral                     | MLV                              | Oral 1 d of age  | important pathogen<br>5–21 d of age | highly susceptible to antibody interference |

Abbreviations: IBR, infectious bovine rhinotracheitis; IM, intramuscular; ND, not done; SC, subcutaneous.

<sup>a</sup> Available in Europe.

of susceptibility,” the time frame in which animals are no longer protected by passive immunity and active immunity has not been stimulated. A promising development has been an IN BRSV vaccine that has been licensed in Europe [34] IN vaccination takes advantage of the poor penetration of antibody from colostrum onto mucosal surfaces providing less interference with the function of vaccines. This vaccine reduced clinical disease in 3-week-old colostrum-fed calves challenged 66 days after vaccination. Another study administered a commercial four-way viral MLV vaccine licensed for parenteral use, intranasally, in 2-week-old colostrum-fed calves and found it to be protective 8 days after vaccination [43]. A single dose of inactivated four-way viral vaccine in 4- to 5-week-old calves protected them against a BRSV challenge 3 weeks after vaccination [46].

#### *Bovine viral diarrhea virus vaccines*

The risk for BVDV infection and disease in young calves seems to be much lower than BRSV. The additional immunosuppression in calves as the result of the BVDV component of many parenterally administered BVDV MLV [59] deserves consideration. Studies conducted on calf ranches have indicated that there is little advantage gained from vaccinating calves younger than 60 days of age [60] and that maternal antibody protection lasts from 70 to 110 days [61]. The greatest risk for BVDV infection was from 4 to 9 months of age as animals were group housed in larger groups [62]. Vaccination programs that vaccinated calves in the first 60 days and then much later at 4 to 9 months were not effective in preventing infection [62]. Based on this information, BVDV control programs that use MLV probably should begin around 2 to 3 months of age and be followed by revaccination after 3 to 4 weeks.

#### *Bovine herpesvirus-1 vaccines*

BHV-1 infections, like BVDV, are unlikely in young calves (Table 1). There are several positive aspects of IN BHV-1 vaccines. Maternal interference is less likely at mucosal sites in young animals, so most of them develop active immunity [41,58]. After IN vaccination, high levels of mucosal and serum interferon are also produced [63] that direct an antiviral effect and may aid in the development of the neonatal immune response. BHV-1 is also immunosuppressive [64]. Because of their localized and limited replication in the nasal epithelium, however, IN BHV-1 vaccines are less of a danger for development of immunosuppression than parenteral vaccines. All BHV-1 vaccines, including IN vaccines [35], can result in latency, which is the ability of the virus to reactivate (recrudesce) and be shed. The biologic relevance of this reactivation and shedding of BHV-1 is unclear because there are no lesions or disease syndromes associated with recrudesence, and the virus can only be reactivated experimentally after several days of treatment with high doses of dexamethasone [35].

### *Clostridial vaccines*

Multistrain *Clostridium* spp bacterin-toxoids are a frequent part of the vaccination program of heifers (Table 1). These pathogens represent the cause of sporadic enteric and musculoskeletal disease. Localized vaccine reactions are the most frequent and have the most serious side effects [65]. Maternal interference significantly inhibited *Clostridial* spp antibody responses in calves vaccinated at 3 [66] or 50 [67] days of age.

### *Mannheimia and Pasturella vaccines*

These bacterial pathogens are frequently isolated from many cases of calf pneumonia and pose a significant threat to heifer development (Table 1). Bacterin-toxoids and avirulent MLVs are commonly used. Bacterin-toxoids have been shown to be inhibited by maternally transferred immunity before 6 weeks of age [36].

### *Mycoplasma bovis vaccines*

This emerging pathogen is also frequently isolated from pneumonia in heifers (Table 1). The current vaccine in common use is a bacterin. At the time of this article, a single experimental vaccine administered at 3 weeks to calves with low *M bovis* antibodies was shown to be protective when calves were challenged 21 days later [68].

### *Salmonella species vaccines*

Although *Salmonella* spp are important pathogen of calves, there are few well-designed control studies in the literature other than field observational studies of *Salmonella* vaccine efficacy. There are three major groups of *Salmonella* vaccines: inactivated with gram-negative core antigens (J-5, J-Vac, and Endovac-Bovi), attenuated live vaccine (Entervene-D), and the subunit siderophore receptor protein vaccines (Table 1). All three vaccine groups have been shown to have efficacy in the field. Only the attenuated live vaccines are labeled for use in calves ( $\geq 2$  weeks old).

### *Rotavirus and Coronavirus vaccines*

These two viruses are common causes of neonatal diarrhea. Maternal antibody dramatically decreases vaccine efficacy [69,70]. Onset of protection against disease and shedding in calves occur before secretory IgA is produced 10 days after vaccination [69], implying that the orally administered vaccine may activate innate immune system in the gastrointestinal tract and decrease disease. These vaccines would be of greatest value for herds with colostrum low in levels of Rotavirus and Coronavirus antibody.

## Summary

Vaccination of heifer calves is complicated by the presence of significant levels of maternal antibody that persist in calves, colostral and neonatal hormonal factors, the lack of full immune competence, and interference in the function of vaccines by the presence of maternal immunity. The first necessity of planning a calf vaccine program is to assess the disease risks at the production site. One must carefully review the antigens that are being used to make sure that they make sense for the operation. The affect of maternal immunity and the age of the animal must be carefully considered in determining the vaccination schedule. The use of MLV-containing immunosuppressive agents should be planned to avoid giving them at times when the animals have low immunocompetence or are immunosuppressed. Using mucosal vaccination routes that minimize induced immunosuppression and interference by maternal antibody is also helpful.

## Acknowledgments

The authors would like to thank Drs. John Butler, University of Iowa, Iowa City, Iowa, Gunilla Blomquist, National Veterinary Institute, Uppsala, Sweden, and David Topham, University of Rochester Medical Center, Rochester, New York for permission to adapt their figures and Clipart Heaven.com, Toronto, Canada for the use of their clipart in Fig. 2.

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