ISVMA 2023 Proceedings
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Cattle Vaccine program development and immunology – a review of immune system physiology and vaccine efficacy. Using evidence based medicine to develop vaccine programs.

Introduction:
Learning objectives:

1. To review vaccine immunology
2. To understand how vaccines stimulate the immune system to protect the host
3. Be able to justify the vaccine recommendations to our clients.

Calves have all the immune components present at birth that they will need as adult cattle but it takes 2 to 4 weeks for these to become fully functional. It takes 5 to 8 months for the immune system to become fully mature.
Due to the syndesmochorial placentation of ruminants there are 6 layers separating the fetal and maternal blood supplies preventing transmission of immunologic components from the dam to the fetus. Therefore, calves are immunologically naïve immediately after birth. Acquisition of passive immunity through colostrum intake helps protect calves from disease in the neonatal period. IgG from colostrum has been reported to have a half-life of 28.5d while IgG from colostrum replacer had a half-life of 19.1d according to Murphy et al (2014). Thus it can be assumed the majority of the immunoglobulins in serum up to 30 days of age are colostral derived. Passively acquired antibody half-life varies between immunoglobulin classes: 16-32 days for IgG1 and IgG2; 4 days for IgM; and 2.5 days for IgA. IgG1 is the most important isotype in colostrum (Kirkpatrick et al 2001).

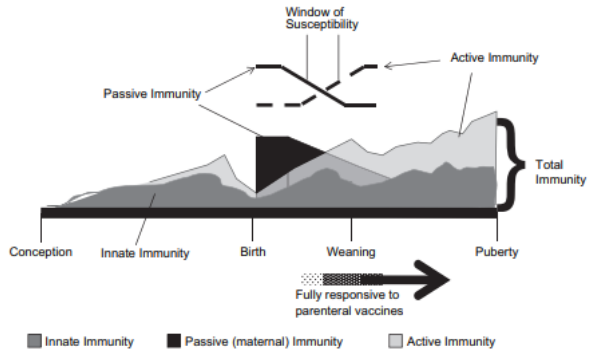

Fig. 1. Development of the immune response in the calf: from conception to puberty. (*Data from* Morein B, Abusugra I, Blomqvist G. Immunity in neonates. Vet Immunol Immunopath 2002;87:207–13; and Butler JE, Sinkora M, Wertz N, et al. Development of the neonatal B and T cell repertoire in swine: implications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

The timing of vaccines administered parenterally requires estimating when the level of maternal antibody is low enough for active immune response to occur sufficiently to provide vaccine immunity. The decay half-life for most maternal antibodies is 16 -28 days. The prime window for vaccination can fall between a few weeks and 8 months (Chase et al 2008). As illustrated in figure 1, this window varies by animal and depends on the level of maternal antibody and vaccine antigen. Antibody levels often decay to a level still high enough to block response to vaccine but not high enough to protect against field infection, creating a window of opportunity for infecting organisms.

For viruses like BHV-1 and BVDV, 3 to 4 months of age is often a good time to administer modified-live vaccine (MLV). BRSV protection is more difficult as maternal interference has been observed in 1- to 6-month old calves. For bacterins , the period of maternal derived immunity interference is often shorter. Intranasal (IN) vaccine have the advantage of being able to replicate in the nasal mucosa and prime mucosal immune system with little interference from secretory antibodies. The mucosal immunity primed by IN vaccines is more likely to prevent infection rather than just reduce disease. Low to no systemic antibodies are detected after IN vaccination.

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

Abbreviations: IBR, infectious bovine rhinotracheitis; IM, intramuscular; ND, not done; SC, subcutaneous.
[a] Available in Europe.

table 1. From Chase et al. 2008

When to vaccinate;
Neonatal calves the mucosal epithelium provides immune function early thus making intranasal and oral vaccines effective in calves less than a week old. Parenterally administered MLV vaccine responses begin at 7-10 days of age. Bacterial parenteral vaccines typically don't have much response in animals less than 3 weeks of ages, except for *Clostridium perfringens* toxoids that have an immune response at 3 days of age.
Calves <3m
Respiratory disease – MLV intranasal vaccines (depends on maternal antibody levels as many MLV IM or SQ are not effective before 30-45 days. Only adjuvanted MLV IM or SC should be used). At branding time in beef calves use adjuvanted MLV IM or SQ or inactivated viral vaccines.
Enteric diseases like rota- coronavirus MLV – 1 dose within the first week of life. These are often interfered with by maternal antibodies. *Clostridium perfringens* toxoid in the first 3-5 days after birth.
Current recommendations are to vaccinate calves prior to weaning or comingling to protect against BRD. No more than 1-2 doses of MLV or 2-3 doses of inactivated vaccines should be given to calves less than 4 months to develop herd immunity against respiratory diseases.
Interval between doses; after vaccination there is response by the T- and B-cells then culling of T- or B-cells that are not useful. This process can take at least 3 weeks. Once the primary response is fully developed the calf can be boostered to get a true anamnestic secondary response (figure 2). In most instances if the primary vaccine is given after 3 weeks of age followed by a booster beyond 3 weeks or even longer will be efficacious. The anamnestic response is better the longer we wait for the booster.

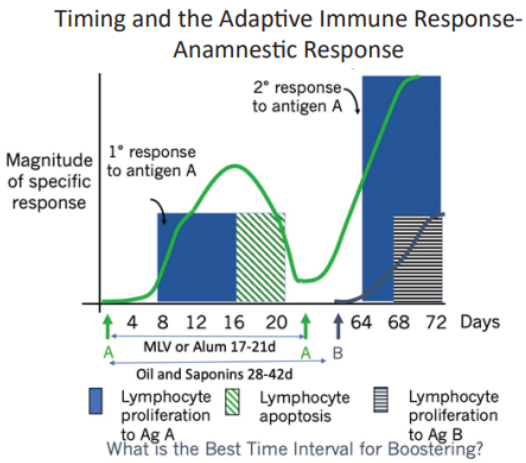

Figure 2. Vaccine primary dose is administered and the booster dose is given 21 days later. (Chase 2021).

Chamorro et al. (2016) found that a single dose of a multivalent MLV vaccine containing BVDV1, BVDV2 and or BRSV administered parenterally or intranasally to calves that received colostrum and are older than 2 weeks can offer some degree of clinical protection against challenge by these viruses later in life when maternal antibodies have disappeared. A single dose of a killed vaccine containing BVDV1, BVDV2 and / or BRSV administered parenterally to calves less than 2 weeks old that got maternal colostrum could offer clinical protection after challenge, however the administration of a second dose after 4 weeks is recommended. In calves less than 2 weeks of age that got maternal derived antibodies given parenteral or intranasal killed or MLV vaccine against these same viruses, may not be protective against clinical challenge later in life. In comparison, administration of parenteral or intranasal MLV to calves deprived of colostrum, primes the B- and T-cell responses and can offer clinical protection to calves after challenge.

Calves > 3m
Respiratory disease – vaccinate 2 to 3 weeks prior to weaning with either 1 dose of MLV or 2 doses of inactivated vaccine. Bacterial respiratory disease vaccine may be used.
At weaning there is immune dysfunction secondary to the stress so delay MLV for a few days to a month. Can use 2 doses inactivated and incorporated bacterial respiratory disease pathogens.
Two – 3 weeks post weaning – give 1 dose MLV or 2 doses inactivated, as well as bacterial respiratory disease if needed.
Heifer development -Respiratory and reproductive disease protection. Heifers need 1 dose MLV prior to adding to the breeding herd.
MLV- 2 doses containing BVDV and BHV-1 in heifers >6 months old and 2 months prior to breeding, or, 2 doses inactivated viral vaccine 5 weeks and 2 weeks before breeding.
Leptospirosis – 2 doses at 5 weeks and 2 weeks before breeding.
Prepartum cows – non-adjuvanted vaccines need to be given within 4 weeks of parturition to get maximum circulating antibody levels for colostrogenesis whereas adjuvanted vaccines can be given earlier in the dry period as they stay high for longer.
MLV – 1 dose. Found to have lower efficacy in preventing PI in subsequent pregnancy and can cause IBR abortions in poorly vaccinated animals. In comparison 1 dose of inactivated vaccine at preg-check time has shown protection for a year against respiratory and reproductive disease in cows and respiratory disease in calves.
Enteric disease in calf including rota- coronavirus, C. perfringens, K99 E. coli. Give 2 doses MLV to heifers, 1 dose for cows at 5 weeks and 2 weeks before calving. Inactivated vaccine requires 2 doses in heifer and 1 dose in cows at 10-12 weeks and 4 weeks pre-calving.

What vaccines can and cannot deliver; vaccines help decrease or prevent disease incidence but are no substitute for good management procedures like nutrition, ventilation and sanitation. Antibodies acquired from passive transfer may block and destroy come antigens in vaccines. However there is still at least 14% of dairy calves in the US that fail to have TPI.

1. Healthy calves respond best to vaccines. Stress from nutritional deficiency (copper, zinc, selenium) environment or disease will result in failure to respond to a vaccine.
2. Timing of vaccination is important. Calves need time to respond to a vaccine before being challenged.
3. Check vaccine labels – one dose or require two. Most killed vaccines require a second dose to be effective.
4. Only use vaccinations necessary for the farm. Unnecessary vaccine cause a metabolic toll.
5. Keep good records. These help ensure everyone gets the vaccines they need and can determine whether protocols are decreasing the incidence of disease and aid health, growth and productivity on farm.

Handle all vaccines properly. Avoid vigorous shaking. Maintain appropriate temperature. Avoid exposure to UV light. Use vaccine immediately after reconstitution. Limit the number of antigens per vaccination event.

According to AABP Vaccination Guidelines, core vaccines for beef and dairy cattle are: BHV-1, BVDV, PI3, BRSV, *Clostridium perfringens, novyi, sordelli, septicum and chauvoei* (*C. hemolyticum* and *tetani* are not considered core).

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