AABP VACCINATION GUIDELINES

EXECUTIVE SUMMARY
This document serves as a reference point for the bovine practitioner for the development of vaccination protocols. The document will aid veterinarians in understanding the scientific literature, vaccine types, potential for adverse events, and reporting mechanisms for product safety issues, and it provides a list of “core” vaccines for cattle. Some information is peer-reviewed and some is based on consensus and the expertise of veterinarians and scientists in the animal health industry, government and private practice.

Sources include current scientific literature on vaccine research and safety issues, information from the USDA Center for Veterinary Biologics for labeling and adverse event reporting, and best quality practices from Beef Quality Assurance programs. Our presentation of “core” vaccines for cattle is based upon consideration of the major infectious agents that require protection in all types of cattle and is designed to meet the AVMA’s definition of what a “core” vaccine should be. The list of “core” agents is not permanent and is subject to change based upon new research, practitioner recommendations, changing production practices, emerging infectious diseases, and other relevant scientific information.

Veterinarians should always follow the guidelines from the governing regulatory agencies where the cattle are located.

PRINCIPLES OF VACCINATION
A standard vaccination program for all cattle operations does not exist. Each individual situation requires evaluation based on the following criteria:

- Risk of disease (anticipated exposure [i.e., impending comingling of different groups], environmental conditions, geographic factors, transportation/handling stress, presence of disease vectors, age, production status, use, and sex of the cattle)
- Consequences of the disease (morbidity/mortality, zoonotic potential, cattle well-being)
- Anticipated effectiveness of the selected product(s) when used in the recommended manner
- Safety: the potential for adverse reactions to the vaccine(s)
- Financial considerations: Cost of immunization (time, labor, lost production and vaccine costs) vs. potential cost of disease (costs of morbidity, mortality, diminished cattle well-being, lost production, and/or restrictions on movement)
- Import and export regulations

Veterinarians should encourage their clients through education and training to have realistic expectations and understand that:

- Vaccination is only one aspect of disease prevention. In the absence of good management, nutrition and husbandry practices directed at animal health and infection control, vaccination alone is not enough to prevent infectious disease.

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Vaccination serves to minimize the risks of disease but cannot prevent illness in all circumstances.

A properly administered, licensed product should not be assumed to provide complete protection during any given field exposure.

Duration of Immunity (DOI) is variable and is impacted by many factors. Among them are:
- Intrinsic factors (age, sex, genetics, other concurrent infections)
- Extrinsic factors (pre-existing immunity from natural infection or maternal immunity)
- Environmental factors (weather, exposure to vectors)
- Management factors (nutrition, hydration, housing, stocking density, level of stress at time of vaccination)
- Disease factors (virulence, infectivity of disease, route of infection, exposure level(s))
- Vaccine factors (type, dose, adjuvant, vaccine schedule, route of administration, co-administration with other vaccines)

Protection is not immediately afforded the patient after administration of a vaccine that is designed to induce active immunity. While some vaccines may provide a rapid non-specific immune response, in many instances, a primary series of multiple doses of a vaccine must be administered initially for that vaccine to induce a specific protective active immunity.

The primary series of vaccines and booster doses should be appropriately administered prior to likely exposure.

Each animal in a population is not protected to an equal degree nor for an equal duration following vaccination.

The immune response to vaccination can be enhanced by natural exposure to particular antigens. This response is not consistent, however, across all animals that have been previously infected or vaccinated. It is not recommended to administer a single dose of vaccine (when labeled for multiple doses) and assume that natural exposure, whether pre- or post-vaccination, will improve the immune response. Follow label directions for full dosing regimens.

All cattle in a herd should be vaccinated at intervals based on label recommendations, or in the absence of specific label recommendations, the professional opinion of the attending veterinarian.

Although rare, there is potential for adverse reactions despite appropriate handling and administration of vaccines.

Vaccine withdrawal times should be observed prior to slaughter.

Cattle should be vaccinated en masse in the same time frame within their cohort groups to optimize herd immunity and protect individuals with poor immune responses.

**INFLUENCE OF MANAGEMENT ON DISEASE**

A well-managed vaccine program can increase disease resistance in groups of cattle. However, immunizations alone are not 100% protective. Management strategies that can minimize pathogen exposure and enhance innate immune function are as important as any vaccination protocol. Disease prevention strategies should be customized for each cattle operation since challenges and management options will vary from one farm to the next.

**Biosecurity and Biocontainment** For pathogens not currently present on the farm, the veterinarian and producer should have a biosecurity plan in place to keep diseases from entering, or, at the very least, be alerted to the introduction of a new disease as early as possible. When evaluating a
farm’s risks for disease exposure, consider the herd’s potential contact with neighboring livestock and wildlife, the condition of new animals entering the facility, animals that leave and return to the facility, and the origin of breeding animals, semen, and embryos. To control the spread of diseases already present on the farm, a biocontainment plan should be followed to minimize their spread.

- **Disease Surveillance** Considering the farm’s management practices, local factors and diagnostic options, each farm should be following a disease surveillance plan. Examples include BVD PI testing, *Mycoplasma* mastitis milk string sampling, routine necropsy of mortalities, *Anaplasma* screening, serological testing, and management of aborted fetuses (diagnostic and disposal plans). As part of the biosecurity plan, the veterinarian should have a reporting system in place that will alert them of unusual, potentially reportable, diseases as well as initial containment steps for the farm to follow until a veterinarian can evaluate.

- **Quarantine** Often a challenge on many facilities, biosecurity plans should include efforts to minimize exposing the existing herd to new arrivals before diagnostic test results are known and/or the high-risk time-period when new arrivals are likely to break with clinical disease has passed. Farms should have protocols for proper biosecurity and disinfection protocols for workers caring for animals in quarantine.

- **Personal Protective Equipment (PPE) and Disinfection** Minimizing transfer of contagious disease from off-farm or between groups of animals on the same facility is critical. Farms should have protocols for visitors to follow when entering the facility, including where on the farm it is appropriate to go, what PPE and boot disinfection will be required, and how appointments are to be scheduled with farm management. Extra precaution should be taken to limit contact with high-risk groups of animals such as very young calves or cows that have recently calved. Conveniently located PPE and appropriate disinfection solutions mixed correctly per label instructions will facilitate protocol compliance.

- **Pest Control** Flies, rodents, wildlife, and domestic animals can all spread disease. Farms should use management practices to control for insect and rodents and minimize wildlife and domestic animal contact with livestock and their feed where practical.

**Optimizing Immune System Performance** Proper nutrition and sound animal husbandry practices can increase a herd’s ability to resist disease when challenged.

- **Nutrition** Ensure the herd has consistent access to a properly balanced diet, both on a macro and micronutrient basis. For confinement facilities, make sure all animals have adequate access to feed. For pasture-based systems, good pasture management can help avoid nutrient deficiencies.

- **Hydration** Ensure that the herd has access to adequate clean safe and palatable drinking water.

- **Overall Health** Diseased animals are less resistant to other disease challenges. Management strategies to control enzootic diseases or excessive parasitism will improve herd health.

- **Housing** Proper housing which allows animals to be comfortable, safe from injury, and protected from weather extremes is a key component of good husbandry. Particular attention should be paid to stocking density, resting surfaces, heat abatement, hygiene,
Historically, the USDA Center for Veterinary Biologics (CVB) used a “tiered” claim system to convey information about the differing levels of efficacy for licensed veterinary vaccines. Vaccines could carry one of the following five claims, depending on the clinical and statistical significance of the presented efficacy data (Veterinary Services Memorandum No. 800.202; June 14, 2002):

- For the prevention of infection (i.e., prevent colonization or replication of the challenge organism)
- For the prevention of disease (i.e., highly effective in preventing clinical disease)
- As an aid in the prevention of disease (i.e., prevent disease to a clinically significant amount)
- As an aid in the control/reduction of disease (i.e., alleviate disease severity, reduce duration, or delay onset)
- Other claims (e.g., reduction of pathogen shedding)

The USDA CVB transitioned to a single-tiered claim in 2015. The agency is now using the following statement for all vaccines: “This product has been shown to be effective for the vaccination of healthy animals X-weeks of age or older.” End-users (veterinarians, producers) can now look up the safety and efficacy data used in the licensure of the vaccine on a publicly available website. Not all efficacy data will be immediately available on the site, as vaccines licensed under the old four-tiered system are not required to post their historical data. However, as vaccines undergo the relicensing process, this efficacy data will be required to be posted on the public website. The purpose of posted efficacy data is to provide the end-user with succinct, non-confusing information about the vaccine’s efficacy and safety, although USDA states that differences in study design and animal air quality and special needs facilities used for high-risk animals.

**Management Protocols for High-Risk Events**

Ensure management practices around high-risk events (shipment, calving, weaning, pen changes, etc.) are such that stress and disruption from normal eating behavior are minimized.

**VETERINARY VACCINE LABELS**

The Virus, Serum Toxin Act is the legal basis for regulations concerning veterinary biologics that are expressed within the Code of Federal Regulations. The requirements for labels of veterinary biologics include:

- Vaccine name (true name, trade names and functional names if applicable).
- Establishment and product code under which the vaccine was produced.
- Product’s indication.
- Minimum age of animals recommended for the product use (unless the product is only used in mature animals).
- Antigen type/strain (if not included in the name).
- Storage temperature recommendations.
- Information about revaccination intervals (i.e., minimum duration of immunity and information about historical revaccination intervals if the product was licensed prior to November 2016; in addition, statements on maternal antibody interference and revaccination during stress or disease exposure may be included).
- Contact information (a veterinarian, potentially in combination with the manufacturer).
- A statement that the product should not be mixed with other products except for as specified on the label.
- Other relevant information (e.g., animal only use statement, statement to contact physician after accidental exposure).

CATEGORIES OF VACCINES

Modified-Live Vaccines Modified-live vaccines (MLV) are products that contain attenuated (weakened) strains of live viruses or bacteria. These vaccines are typically produced in cell cultures that produce a live, weakened pathogen that is still able to replicate in the animal, but should not cause clinical disease. Due to this ability to replicate, modified-live vaccines generally stimulate a longer lasting immunity across a wider range of antigen strains than killed vaccines. Modified-live vaccines do not require the use of adjuvants to stimulate an immune response and are less likely to cause tissue and allergic reactions than killed products. Some of the potential disadvantages to modified-live vaccines are mutation to a more virulent form (return to virulence—an extremely rare event that should not impact the selection to use these products), adventitious agents (viruses or bacteria that contaminate the vaccine), exacerbation of disease in animals with compromised immune systems, and a significant risk of abortion or transient infertility when used in naïve animals6, 7 (see Adverse Events section for further explanation on this topic). Modified-live products are usually supplied in a lyophilized dry powder that needs to be mixed with a sterile diluent prior to use in cattle. Modified-live vaccines need to be stored properly per manufacturer recommendations and kept out of direct sunlight and heat. Once reconstituted, these products need to be used immediately. There are no evidence-based recommendations in the literature for veterinary vaccines in terms of time frame of viability post-mixing, so following manufacturer directions on usage is strongly recommended.

Killed Vaccines Killed (inactivated) vaccines contain either whole killed viruses or bacteria or parts of these organisms (subunit vaccines). Toxoids are a subset of non-living vaccines that contain modified forms of toxins that are immunogenic but not toxic. The viruses or bacteria used in these products are typically killed by heat or chemicals (i.e., formaldehyde). These killed antigens, when injected, may not stimulate an effective immune response alone, so an adjuvant is added to the product. Adjuvants have several activities including enhancement of immune system antigen presentation and activation. Killed vaccines are safer than modified-live vaccines in that they have no risk of return to virulence, no living adventitious agents, and, for agents that cause reproductive loss, they have lower risk of adverse reproductive events than MLV. It is generally accepted by practitioners that killed products are more durable in storage than modified live vaccines, and that multidose vials of killed products can be stored after opening (i.e., repeated needle penetration) for use later. There are no published data to support these claims, however, and labeling on killed products indicates the entire vial should be utilized when opened. In general, killed products are less likely to stimulate a long-lasting immunity compared to modified-live products, and therefore need more frequent booster doses. This duration of immunity can be extended depending on the adjuvant used, and in some cases, killed vaccines can provide long lasting immune responses similar to modified live products. Given the addition of adjuvants to these vaccines, tissue reactions after vaccine adminis-
tration are more common when giving killed products. Hypersensitivity reactions, anaphylaxis, and death are also experienced more frequently with killed vaccines.

Mucosal Vaccines Mucosal vaccines are products designed for administration directly onto the mucus membranes, typically orally or in the nostrils. The bacteria or viruses used in these vaccines are modified-live and provoke a localized immune system reaction that promotes the production of nonspecific immune products such as interferon, and antigen specific secretory IgA (sIgA) and sIgG antibodies, and in most cases systemic IgG. This antibody production helps reduce the risk of infection via these mucosal sites. These vaccines are relatively safe for newborns through adults, and in most populations, seem to have low risk of adverse reactions. Currently, available mucosal vaccines seem to be safe for administration to pregnant animals without risk of abortion, and maternal antibodies may be less likely to interfere with mucosal vaccines, as compared to parenteral vaccines, when delivered to young cattle. Generally speaking, these vaccines can be expected to provoke a more immediate immune response and protection from disease compared to parenteral killed or modified-live vaccines, but the immunity generated is not as long lasting as the injectable vaccines. Live mucosal vaccines are more likely than parenteral vaccines to be shed from vaccinated individuals to other in-contact cattle.

Conditionally Licensed Vaccines Conditionally licensed vaccines are products produced by manufacturers for limited markets, emergency situations, local circumstances or other special instances. These products must meet the same safety and purity requirements as fully licensed vaccines, however, unlike fully licensed products, they only need to provide a “reasonable expectation” of efficacy, and a full potency test may not be mandatory. Licenses for these products are typically issued for a finite time frame, generally one year in length, but this time can vary depending on the product.

Autogenous Vaccines Autogenous vaccines are killed or subunit custom-made products from herd-specific pathogens. These vaccines must be produced under a veterinary-client-patient relationship by a facility licensed with the USDA Center for Veterinary Biologics, and under conditions that promote safety, purity, and potency of the product. Autogenous vaccines are permitted for use when no currently licensed product is available to provide protection, or currently licensed products do not provide protection. While these vaccines are created for use for the herd of origin, they can be utilized by herds adjacent to the herd of origin upon notification of the CVB and state regulators. Non-adjacent herds may also use autogenous vaccines with the express permission of the state veterinarian prior to shipment, and the CVB must be notified. Autogenous vaccines can be used up to 12 months from the harvest of the first serial, or 15 months from the date of isolation, whichever comes first. The use of autogenous isolates can be extended to 24 months if the attending veterinarian demonstrates continued need for the vaccine by providing updated diagnostic information from the herd of origin and provides evidence on the satisfactory protection from the previous use of the autogenous biologic. Extending the use of the autogenous product beyond 24 months requires special permission from the CVB and additional product testing.
ADVERSE EVENTS

The purpose of this section of the guidelines is to provide a brief background on adverse events and adverse event reporting related to vaccines and vaccination, to focus on some general recommendations for avoiding adverse events, to address some specific types of adverse events encountered in bovine practice, and to provide additional information resources.

Background

Vaccination is only one part of an effective immunization program. Immunization involves a complex set of interactions between the animal’s immune system and the vaccine. The animal’s immune system itself is impacted by a myriad of factors including age, nutritional status, and the environment. The safety and efficacy of the vaccine is also impacted by its type, handling and administration.

Given the complexity of these interactions between the animal, the environment, and the vaccine, the potential for the occurrence of adverse events with vaccines is ever present. From our colleagues in the companion animal world, current knowledge supports the statement that “No vaccine is always safe, no vaccine is always protective, and no vaccine is always indicated.”

Veterinary immunological products are currently almost exclusively regulated by the USDA Center for Veterinary Biologics (CVB). Veterinary immunologicals include both vaccines and products designed to diagnose disease such as ELISA kits. For the purposes of these guidelines, the focus will be on vaccines.

Prior to June 2018, manufacturers of veterinary vaccines were required to monitor the performance of their products for safety and efficacy and to respond to the CVB in specific situations in which the agency had reason to believe there was a safety or efficacy problem related to the product.

After June 2018, the USDA formalized biological adverse event reporting by publishing regulations in the Federal Register and by issuing policy guidelines. The pertinent definitions were captured in 9 CFR 101.2.

Definitions

The regulation defines an adverse event as “Any observation in animals, whether or not the cause of the event is known, that is unfavorable and unintended, and that occurs after any use (as indicated on the label or any off-label use) of a biological product, including events related to a suspected lack of expected efficacy” and further defined as “…any undesirable occurrence after the use of an immunobiological product, including illness or reaction, whether or not the event was caused by the product.”

From a practical perspective as veterinarians, adverse events can be put in two broad categories:

**Adverse Reactions**

Local reactions such as those at the injection site and generalized reactions ranging from elevated body temperatures and loss of appetite to mild hypersensitivities, severe anaphylaxis, abortion or death.

**Lack of Expected Efficacies (LOEs)**

Failure of the product to work as expected.

Adverse Event Reporting

A key first step in reporting an adverse event is to contact the manufacturer of the product. They have a responsibility to report the event to the CVB and it is in their best interests to address the report of the performance of their product proactively. Key elements of information the manufacturer will need will include a concise but complete history of the event to include:

- The animal(s) involved including the number vaccinated and number reacting.
- The product(s) involved including, if possible, the lot/serial numbers of the products.
Avoiding Adverse Events with Vaccines A multitude of factors contribute to the frequency of adverse events including systemic and local adverse reactions and unexpected lack of efficacies (LOE). Many of these factors are out of the practitioner and producer’s control (i.e., weather) but can nevertheless be considered in designing and implementing vaccination protocols:

- Disease Prevalence/Risk: Reduce or eliminate the use of vaccines in areas of low prevalence for particular diseases, and/or in situations of low risk.

- Weather
  - Vaccination when the ambient temperature is high appears to increase the likelihood of adverse events, both systemic reactions and LOEs. Beef Quality Assurance (BQA) guidelines recommend avoiding working cattle when the Temperature Humidity Index (THI) is over 83°F as a standard practice.\(^\text{12}\)
  - Vaccination when animals are wet from snow or rain will increase the likelihood of injection site reaction complications.
  - Both intense cold and heat will complicate vaccine handling:
    - Heat and UV light contribute to vaccine compromise and lack of efficacy.
    - Freezing, especially of bacterins, will increase the possibility of adverse reactions, including anaphylaxis.

- Breed
  - Anecdotal reports suggest that dairy breeds and some purebred beef breeds tend to have increased systemic reactions to Vibrio-Lepto combinations.
  - Anecdotal reports suggest that dairy breeds and some purebred beef breeds are less tolerant of the use of multiple Gram-negative vaccines at one time.

- Other factors, such as stress, previously mentioned in this document.

GUIDELINES FOR SPECIFIC SITUATIONS

Expected and Unexpected Responses to Vaccination Activation of the immune system in response to challenge, whether a wild-type challenge or a vaccination, has a biological cost.
This cost is reflected in potential expected, but variable, responses to vaccination which may include:

- Elevated body temperature
- Mild and transient malaise/depression
- Temporarily lowered feed consumption
- Temporary drop in production parameters

While normal, the degree to which these reactions occur, and their duration, may be unexpected and may be viewed as an adverse experience/event.

**Hypersensitivity/Anaphylaxis** Hypersensitivity and anaphylaxis are potential outcomes of any vaccination event. In addition to the general steps to reduce and mitigate adverse events:

- Familiarize producers and vaccination crews with the signs of hypersensitivity/anaphylaxis in cattle.
- Incorporate the practice of carefully observing cattle post vaccination for signs of hypersensitivity, at minimum 30 minutes post-administration.
- Where appropriate, within the constraints of a VCPR, ensure that producers have the equipment, medications, and materials to respond to an anaphylactic event.
- Properly store vaccines. Killed vaccines are particularly likely to cause adverse reactions if they have been frozen.

**Injection Site Reactions** Injection site reactions are an inherent risk of vaccination. The risk is generally higher with killed vaccines due to the adjuvant and varies with the type of adjuvant and with the antigen. Injection site reactions can be minimized by following the manufacturer’s label directions and Beef Quality Assurance (BQA) guidelines. Most injection site reactions are not necessarily a function of the vaccine but of vaccine handling and administration. These can be minimized by:

- Avoiding vaccinating when animal’s hides are wet.
- Avoiding vaccinating in areas of hide that are contaminated by manure or debris.
- Avoiding contamination of multi-use vaccine vials. Never place a needle which has been used to inject an animal back into the vaccine bottle.
- Preventing contamination when mixing vaccines.
- Changing needles frequently while vaccinating (ideally between every animal).
  - Always have a sharp needle.
  - Do not use a damaged or burred needle.
- Vaccinating subcutaneously whenever possible and always in the neck triangle outlined in BQA. Avoid vaccinations in the rump, tail head, or too far back on the shoulder. Avoid intramuscular injections unless that is the only labeled route and then vaccinate only in the neck region.

**Use of Modified Live IBR and BVD Vaccines** The use of MLV vaccines in cattle has generated controversy since the practice of using these vaccines began. Discussion of the relative safety and efficacy of killed and MLV vaccine had been ongoing, with a consensus that a MLV vaccine would be, on average, more efficacious, and a killed, on average, safer. However, the controversy intensified with the granting of the “safe in pregnant cow/nursing calf” label claim by the USDA CVB in 2003.

Regarding use in pregnant cattle, there are currently two concerns that involve two very different disease syndromes, one caused by Bovine Viral Diarrhea (BVD) Virus and one by Infectious
Bovine Rhinotracheitis (IBR). These two issues illustrate the classical biological tradeoff between efficacy and safety:

- **BVD Efficacy** How effectively will the vaccine prevent the development of a persistently infected (PI) calf in the vaccinated dam?
  - While BVD infection has an overall impact on animal health as a cause of immune compromise, respiratory and enteric disease, and reproductive compromise, PI calves are one of the most easily documented and visible manifestations of the disease.
  - Effective vaccination programs cannot eliminate all PI calves but can contribute greatly to a successful BVD control program.
  - To date, MLV BVD vaccines have, in general, been found to be more effective than killed in preventing PI calves.13,14

- **IBR Safety** Can the modified-live vaccine cause a pregnant animal to abort or negatively impact reproductive performance?
  - Yes, administration of MLV IBR fractions to naïve animals or those vaccinated with killed IBR fractions can cause a significant number of abortions and low conception rates.15
  - Administration of MLV IBR fractions to cows and heifers previously vaccinated with an MLV IBR vaccine, prior to breeding, can lead to decreased conception rate from AI service.22 Total breeding season pregnancy success was not affected by use of MLV vaccines in this study.22 It should be noted this study monitored conception rates in cattle vaccinated with MLV vs killed fractions of IBR vaccines without a noted disease challenge from IBR.
  - The use of MLV IBR vaccines should be carefully evaluated by the practitioner for safety of administration to pregnant cattle, naïve cattle, and cattle entering the breeding season, to determine the risks and benefits of MLV vaccination in the face of varying disease challenge.

For several reasons, the MLV vaccines contain both of these two viruses, and are likely to remain so because of:

- The way these vaccine labels were approved for reproductive disease by CVB (treating IBR and BVD similarly although for different reasons).
- The development of multivalent vaccines to meet the needs of the client.
  - Practical constraints of the economics of both cattle and vaccine production
  - Human behavior
  - Administering one vaccine containing both viruses is better than two separate vaccines each containing a single virus.
- One time through the chute is better than two.
  - There are currently no monovalent IBR or BVD (Type 1 and 2) MLV vaccines labeled for fetal protection (FP).

Given the linkage between these two viruses, the way forward is to use these vaccines in the manner that is most likely to contribute to their efficacy and place them in programs that will aid in meeting the challenges that the individual producer and production system face.

In addition to all the animal husbandry steps necessary to set up an animal for effective immunization and proper vaccine handling, vaccination recommendations include:16

- Prior to the first time the cow or heifer is vaccinated with an MLV IBR or BVD while pregnant, they should have been vaccinated while open 30-60 days prior to breeding with the appropriate MLV labeled for FP.
In heifers:
- The vaccination 30 to 60 days prior to breeding should be the second FP vaccine the animal receives. Heifer development should ideally employ the use of MLV BVD and IBR vaccines.\(^{24}\)
- This initial FP vaccination should be given when it is unlikely that there will be interference from maternal antibodies. In most instances this would be when the calf is greater than 4 months of age.
- The vaccination should be at an age when the heifer’s immune system is likely to respond to the vaccine.
- The vaccine should be boosted annually.

**GRAM-NEGATIVE VACCINE STACKING**

Endotoxins are components of Gram-negative bacterial cell walls (lipopolysaccharide, peptidoglycans, lipoproteins). All whole cell vaccines against Gram-negative organisms—almost exclusively bacterins—contain some level of endotoxin resulting from the manufacturing process. In properly manufactured and handled vaccine, most of this endotoxin is bound, not free. Vaccines containing whole cell preparations of the following antigens will likely have some level of endotoxin:
- *E. coli* (rough mutant vaccines for mastitis, not K99 pili vaccines)
- *Salmonella*
- *Histophilus*
- *Moraxella*
- *Campylobacter*
- *Pasteurella*
- *Mannheimia*

Some vaccines for Gram-negative bacteria contain purified outer membrane proteins, pili or fimbriae (subunit vaccines) and thus incorporate far less endotoxin and largely do not contribute to endotoxin stacking. Refer to manufacturer labels for specific details.

To avoid the potential adverse effects of endotoxin the following steps are recommended:\(^{19}\)
- Handle all vaccines properly.
- Avoid vigorously shaking all vaccines, especially bacterins.
- Maintain at the appropriate temperature—freezing can result in the release of bound endotoxin.
- Avoid exposure of bacterins to UV light, which can increase concentrations of endotoxin.
- Do not use vaccines after the expiration date has passed.

**Limit the number of antigens per vaccination event.**
- Dairy and beef breeds should be limited to no more than one Gram-negative antigen at a time.\(^{19}\) Using two or more Gram-negative antigens at one time increases the risk of toxicity.\(^{19}\) Use of multiple Gram-negative agents at one time can lead to increased risk of death.\(^{21}\)
- Administer vaccines on opposite sides of the neck.

**Use of Vibrio Combinations in Dairy Cattle**

There is a slight risk of increased hypersensitivity reactions including abortion with the use of *Campylobacter* (Vibrio) combination vaccines in dairy cattle.\(^{20}\) This risk can be mitigated by using a monovalent vaccine and by using such vaccines only in situations where the risk of vibrio outweighs the risks of reactions. Please consult the manufacturer when utilizing these products.
VACCINE STORAGE, TRANSPORT, HANDLING, AND ADMINISTRATION

Storage and Transport Proper handling and storage of veterinary biologicals is imperative to ensure the effectiveness of the product and its benefit to the animal to which it is administered. In accordance with Centers for Disease Control and Prevention (CDC) guidelines, this section will briefly explain the principles to vaccine storage and handling pertinent to cattle in the U.S. From the time the vaccine product leaves the manufacturer to the point of administration, there are many potential areas for failure that can lead to poor product potency and thus provide a poor immunological stimulus.

For a complete guide on vaccine storage and handling, review the Vaccine Storage and Handling Toolkit found on the CDC’s website.17

Storage

- Most vaccines used for cattle production in the U.S. are to be stored in refrigeration temperature, 35-45° F (2-7° C). A few vaccines must be kept frozen until use.
- Products should be placed into their proper storage temperature as soon as arriving to the veterinary clinic, farm or ranch.
- Vaccines should not be stored within the door of refrigerators. The temperature variance is highly exaggerated in the door and can be too warm for proper storage.
- Vaccines should be placed within the center of the body of the refrigerator. Refrigerated products should be stored far enough away from the freezer portion (if equipped) to prevent potential freezing of the product.
- If using a household refrigerator, water bottles within the doors and top and bottom shelf can assist in keeping the interior temperature more stable during frequent use.
- Refrigerators designed and marketed for vaccine storage may have different manufacturer recommendations compared to household refrigerators.
- Vaccines should remain in the original packaging until use. Rotate the oldest products to the front for faster use or use of the shortest expiration date.
- Refrigerators used for vaccines should not store food, drinks, or other products for human consumption. Please refer to the Occupational Safety and Health Administration for more complete information on this regulation.
- Temperatures within a refrigerator are best monitored with a high-quality thermometer with the probe placed centrally in the body of the refrigerator.
- For best product storage, the temperature of the refrigerator should be logged on a regular basis. The CDC recommends twice daily—at the start and end of a workday.
- Logging refrigerator temperature can assist in providing a start point to adjust the refrigeration unit, or to identify and repair the refrigeration unit.
- During power outages, the refrigerator should not be opened until power has been restored. After power is restored, the temperature should be checked and logged in the appropriate logbook or sheet. Any vaccines affected should be recorded and the manufacturer contacted as needed for further guidance.
- The length of power outage may dictate whether a product is useable or if the product should be moved to a proper storage location or apparatus until power is restored.
- There are no known standards reported that can dictate whether a product is inactivated by inadequate storage temperature and can
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Vary based on the pathogen, strain, vaccine carrier, storage container, light exposure and manufacturer.

- In general, vaccines should remain away from sunlight exposure as much as possible until immediately before use.
- The appearance of a product is not a reliable indicator of being stored at the appropriate conditions.

Transport
Bovine veterinary medicine lends a great frequency to the transport of vaccines and biological products. When transporting biologicals, care should be taken to reduce risk of product failure at all times.

- Vaccines should be maintained in cold storage during transport.
- Insulated coolers or portable refrigeration units are ideal for transporting vaccine products.
- Insulated coolers with frozen ice packs should maintain refrigeration temperature between 35-45 °F (2-7 °C).
- Temperature logging should be performed when transporting products.
- Ice packs in insulated coolers should not be in direct contact with the product. A layer of insulation should be placed between the products and the frozen ice packs to prevent unnecessarily freezing the vaccines.
- Insulated coolers containing vaccine should be stored appropriately within a vehicle cabin, as the temperature in a trunk or truck bed may be too hot or too cold depending on the season and area of the country. Storage within traditional veterinary mobile unit boxes may become extremely hot in the summer while cold in the winter without the engine running.
- Never transport more vaccine than is necessary for the job or time allotted. This reduces the risk of shock on any stock vaccine stored at a clinic or farm.
- Never shake to mix vaccines nor expose them to direct sunlight or extreme temperatures, especially during transport.

Handling and Administration
Handling of vaccines after transport and administration of these products is always recommended to follow aseptic techniques for mixing and dosing, while following BQA guidelines.

- A new, sterile needle should be used to puncture a vaccine product vial. Using dirty or used needles is never recommended when puncturing a new vaccine vial or when drawing out multiple doses from a multi-dose vial.
  - Inserting dirty or used needles into a previously punctured vial can introduce bacteria and debris into the vaccine.
  - Such contamination of multi-dose vials can lead to increases of immunization failure and injection-site reactions.
- When mixing a vaccine product with two components, a new, sterile needle and syringe should be used to draw up diluent and place into the subsequent dried powder vial. Alternatively, a new, sterile transfer needle can be used to mix vaccine products.
- Never reconstitute a vaccine until ready for use. Follow manufacturer recommendations per label directions on how rapidly reconstituted vaccines should be used post-mixing.
  - Reconstituted and ready-to-use vaccine products should remain out of direct sunlight and in a cooler until immediately before use. This ensures the highest possible stability given conditions of the time of year, climate, time of day and working environment.
- Vaccines used in cold, winter months may still be stored in a cooler until immediately
AABP VACCINATION GUIDELINES

before use to control temperature from freezing point. Frozen vaccines can be ineffective just as vaccines that are too warm.
- Multi-dose vials, when opened or punctured for product withdrawal, should not be stored for later usage per USDA CVB recommendations. These products should be discarded.
- Reconstituted vaccines should not be kept after mixing. Such products that have been reconstituted should be properly disposed of after use.
- Standard sharps safety procedures should be followed when mixing, drawing-up, and administering vaccine products. Refer to the Occupational Safety and Handling Administration for a complete guide on sharps and biohazard safety.
- Take precaution in mixing and administering *Brucella abortus* vaccines, given that they are a live vaccine and have zoonotic disease potential.
- Use of syringes and needles during mixing and administration should follow aseptic techniques.
  - Label vaccine syringes and coolers when using the products in the field.
- Discard single-use plastic syringes after use.
- Automatic syringes can allow rapid administration, but aseptic techniques should be followed when handling and cleaning these syringes.
  - Automatic syringes should be cleaned after use. Cleaning should include rinsing, washing with mild detergent and allowing to air dry. When reassembling automatic syringes, the syringe may be flushed with sterile water before use to remove any residual detergent.
  - It is not recommended to rinse syringes with disinfectants, as these solutions can inactivate vaccines.
- During use, vaccines should remain in a cooler until immediately before use.
- Always follow label directions.
  - Many vaccines need a booster within 3 to 4 weeks after the initial dose.
  - Products requiring a booster will not achieve full immunity if only an initial dose is given without the corresponding booster dose.
  - Read each product label carefully before choosing and incorporating products into your immunization protocols.
- Proper BQA guidelines for administration will include the following:
  - Draw from the vial with a sterile needle.
  - Use high quality syringes (either single use or reusable).
  - Inspect the working area for user safety in a chute, headlock, stanchion or other environment used for cattle handling.
  - Administer the correct dose per label directions.
  - Use the smallest needle possible that ensures speed but also good product flow.
  - Administer through the correct route:
    - IM intramuscular
    - IN intranasal
    - SQ subcutaneous
    - IV intravenous
  - Never give IV medications by a different route of administration. Such use can result in violative residues.
  - Administer in the recommended area of the animal:
    - Triangular area in front of the shoulder slope
  - Change needles frequently:
    - Ideally, a new needle per animal provides the lowest risk of disease transmission and contamination.
    - A new needle for each animal is not always feasible or practical in certain situations.
AABP VACCINATION GUIDELINES

- Needles are designed to be single-use products and contain a coating that assists in gliding during administration. Multi-use of a single-use needle will dull the needle, lose the assisting coating, and result with increased risk of tissue damage.
- Follow the correct withdrawal times for slaughter as stated by the USDA on the product label. The basis for vaccine withdrawal times as determined by USDA APHIS is due to local inflammatory reactions from injection, and not based on potential violative antibiotic residues.
  - 21-day withdrawal: water-based vaccines
  - 60-day withdrawal: oil-based vaccines
- Never administer vaccine products in areas other than the neck.
- Never market an animal that contains a broken needle shaft.

HUMAN SAFETY RISKS
Use of vaccine products in the field can pose a potential human safety risk. To ensure a reduction in risk of injury, please take the necessary steps:
- Ensure all chutes, headlocks, stanchions, alleyways and processing equipment are in proper working condition and are well-maintained.
- Ensure that all grease joints are well lubricated.
- Notify all personnel of potential pinch points in cattle-handling equipment.
- Maintain good cattle handling techniques.
  - Low-stress handling is recommended.
  - Excessive shouting, use of prods and electric shock, and poor cattle stockmanship can increase risk of human and animal injury.
- Label all biohazard and sharps containers appropriately.
- Purchase approved containers for disposal of needles and biohazards such as unused vaccine and used syringes.
- Dispose of biohazard containers through proper channels.
- Ensure that needles are contained and not left on syringes without being re-capped in a safe manner, or disposed of into a sharps container.
- Needle recapping should be done carefully, ideally with pliers or the one-handed scoop technique.
- Alternately, syringes with needles attached can be disposed of whole into a sharps container, without the need for recapping.
- Seek medical attention from a physician if accidental injection occurs with a used needle or with a vaccine product.
- Never assume that you are completely risk-free from needle stick injury.
- Report the human exposure immediately to the manufacturer of the vaccine. Most will have a defined process for providing information through a call center designed to respond specifically to human exposures to their products and to interact with human health care professionals.

CORE VACCINES: GENERAL
The AVMA defines core vaccinations as those “that protect from diseases that are endemic to a region, those with potential public health significance,
required by law, virulent/highly infectious, and/or those posing a risk of severe disease.

Core vaccines have clearly demonstrated efficacy and safety, and thus exhibit a high enough level of patient benefit and low enough level of risk to justify their use in the majority of patients.”

The following bovine vaccines meet these criteria and are identified as “core” in these guidelines, for all beef and dairy cattle:

- Infectious Bovine Rhinotracheitis virus (IBRV) (Bovine herpesvirus 1)
- Bovine Viral Diarrhea Virus (BVDV)
- Parainfluenza Virus (PI3)
- Bovine Respiratory Syncytial Virus (BRSV)
- Clostridial Vaccines (C. hemolyticum and tetani not considered core but included as part of the discussion in Risk-Based Vaccines)

Because these are considered “core” the commercial preparations contain similar antigens and the labels for IBRV, PI3, BVDV and BRSV are very similar:

- Killed
  - Require two vaccinations 3 to 6 weeks apart, depending on the label, to be effective.
  - Are labeled to be repeated after 5 or 6 months of age.
  - Require annual revaccination—additional data should be considered in designing protocols.
  - Multiple antigen combinations.

- MLV
  - All MLV vaccines containing IBRV and BVDV would have the same restrictions regarding use in pregnant cows and cows nursing calves.
  - Usually labeled for a single dose administration for respiratory disease.
  - Annual revaccination recommended.
  - May be repeated at variable intervals to increase the percentage of animals responding or to meet anticipated challenges. This interval needs to be at least 3 weeks if the goal is an anamnestic response.
  - Immune response may be negatively impacted by presence of maternal antibody—a variable impact.
  - Generally recommended to be boosted after 5 to 6 months of age.

- Combination
  - According to Walz et al,24 the combined use of MLV and killed vaccines in heifer development programs can lead to effective fetal protection. The administration of two doses of MLV IBR and BVD antigens, followed up later in life with boosters using killed IBR and BVD antigens, provides protection from fetal loss for these two diseases. This is technically an off-label administration of the vaccine regimens in the U.S., but is licensed for this purpose in Europe.

SPECIFIC VACCINES

Infectious Bovine Rhinotracheitis Virus (IBRV)
Disease Considerations  IBRV, or Bovine Herpesvirus 1 (BHV 1), is a highly contagious virus that is ubiquitous in the cattle population. The virus can cause respiratory disease alone or as part of the BRD complex; and can cause reproductive disease including abortion, as well as conjunctivitis and encephalitis. From a practical perspective, vaccination programs are designed to primarily address the virus’ contribution to the BRD complex in all classes of cattle, and the reproductive effects, principally abortion, in breeding animals.

Although there are monovalent IBR vaccines available, most are used in combination with other antigens to meet various production needs.
**AABP Vaccination Guidelines**

- **Vaccines**
  - **Killed**
    - Are safe from reproductive adverse effects in pregnant cows and could be used in calves nursing pregnant cows without having a reproductive impact on the dam.
    - Only one product is labeled for protection against IBR abortion.
  - **Modified Live Parenteral**
    - May cause major adverse reproductive effects in breeding animals if the animal's immune system is not prepared to protect the animal or the fetus. Effects (<10%) on conception rate have been seen in animals “properly vaccinated” 37 days and less prior to breeding. Animals may be protected to some variable degree through wild type exposure or more effectively through an appropriate fetal protection vaccination program with a vaccine labeled for fetal protection:
      - Prior to the first time the cow or heifer is vaccinated with an MLV IBR or BVD while pregnant, they should have been vaccinated while open 30-60 days prior to breeding with the appropriate MLV labeled for FP.
      - In heifers:
        - The vaccination 30-60 days prior to breeding should be the second FP vaccine the animal receives.
        - This initial FP vaccination should be given when it is unlikely that there will be interference from maternal antibodies. In most instances this would be when the calf is greater than 4 months of age.
        - The vaccination prior to breeding should be at an age when the heifer’s immune system is likely to respond to the vaccine, which is likely 9 months or older.
  - **Chemically altered temperature-sensitive variant**
    - Safe from reproductive effects in pregnant animals.
    - Requires two doses initially 4 to 6 weeks apart.
    - Labeled for fetal protection.
  - **Modified Live Intranasal**
    - Not labeled for fetal protection.
    - Labeled to be repeated after 5 months of age if vaccinated prior to that time frame.
    - Available in combination with MLV PI3.
  - **Chemically altered temperature-sensitive variant**
    - Not labeled for fetal protection.
    - Available in combinations with PI3 and PI3/BRSV.
    - Some products labeled for use in 3-day old to 1-week old calves.

- **Vaccination Schedule Notes**
  - IBR is one of the antigens most commonly given to increase the percentage of individuals in a population with an adequate immune response. If an anamnestic response
in the population is also a goal, this vaccination needs to be scheduled at least 3 weeks post the initial vaccination.

**Outbreak Mitigation**
- IBR is often a contributor to the BRD complex. Both individual and group antibiotic treatment may be indicated to mitigate the effects of the associated bacterial component.
- Vaccination in the face of an outbreak may be helpful in some situations.

**Other** Infection with a wild-type herpesvirus will result in a latent infection after the animal recovers from the actual infection. When stressed, the latent virus may recrudesce and be shed. Vaccination may also result in a latent infection with the vaccine virus. This tendency to go latent varies with the vaccine strain. The clinical significance of recrudescence is poorly understood.

**BOVINE VIRAL DIARRHEA VIRUS (BVD)**
Disease considerations: BVD vaccination programs are designed to primarily address the virus’ contribution (immunosuppression) to the BRD complex in all classes of cattle, and the reproductive effects of abortion, fetal resorption, congenital malformation of the fetus, and the birth of calves persistently infected (PI) with the virus in breeding cattle. Because of the genetic diversity of the virus, all vaccines depend on some degree of cross protection. Although there are two monovalent BVD vaccines available (killed and MLV), most BVD vaccines are in combination with other antigens to meet various production needs. This combination means the same general principles of vaccination that apply to IBR apply to BVD (see the sections on Adverse Events and on IBR for a more complete discussion). It should be noted that, in contrast to multiple published clinical trials testing BVDV vaccination for fetal protection, no clinical trial has specifically evaluated the efficacy of BVDV vaccination to decrease naturally occurring BRD morbidity or mortality. Benefits of BVDV vaccination for BRD control are assumed based on experimental challenge studies.

**Vaccines**
- **Killed**
  - Are safe from reproductive adverse effects in pregnant cows and could be used in calves nursing pregnant cows without having a reproductive impact on the dam.
  - None are labeled for fetal protection; one is labeled for the prevention of PIs.
- **Modified Live**
  - Attenuated
  - All contain BVD Types 1 and 2.
  - Some are labeled for fetal protection.
  - Vaccine contains the same safety warning as vaccines containing the attenuated MLV IBR.

**Outbreak Mitigation** Taking steps to limit exposure such as eliminating PI animals from the impacted group are critical. Initiating a BVD control program under the guidance of a veterinarian may mitigate future losses.

**Other** The ability of the virus to persistently infect a fetus and newborn calf, the longevity of some of these PI calves, and the resulting exposure to other animals up through the Stocker and feeder phase and pregnant females make BVD control a challenging situation impossible to completely control with vaccination alone. It is important to recognize that the presence of a PI animal effectively eliminates the possibility of achieving herd immunity for BVD, even in the face of vaccination. The constant shedding of virus from body fluids coming from PI animals forces the Reproductive Number ($R_0$)—the number of
susceptible animals that one infected animal can infect) to infinity. Effective BVD control programs combine vaccination, testing for PI status (and elimination of positive animals) and biosecurity, and the veterinarian has a key role in developing these programs.

**BOVINE RESPIRATORY SYNCYTIAL VIRUS (BRSV)**

**Disease Considerations** BRSV is a specific viral respiratory disease of cattle of all ages, including nursing calves and adult cows. Clinically, BRSV infection may be indistinguishable from other viral infections associated with the BRD complex. Exacerbation of clinical signs has been documented when concurrent BRSV and BVD or IBR infection exists. A significant contributor to pathology resulting from BRSV infections is the immune response.

■ **Vaccines**
  ● Killed
    □ Require two vaccinations 3 to 6 weeks apart, depending on the label.
    □ Labeled to be repeated after 5 or 6 months of age.
    □ Annual revaccination is recommended.
  ● Modified Live Parenteral
    □ Attenuated
    □ Immune response may be negatively impacted by presence of maternal antibody.
    □ Usually labeled for a single dose administration.
    □ No monovalent vaccine is currently available.
  ● Modified Live Intranasal
    □ Attenuated
    □ In combination with chemically altered temperature sensitive IBR and PI3. Some combinations include non-temperature sensitive IBR.
    □ Labeled for use in 3-day old to 1-week old calves, depending on label.

■ **Vaccination Schedule Notes**
  ● Frequency of vaccination with the modified live intranasal is variable—consult with manufacturer’s technical services.

■ **Outbreak Mitigation**
  ● BRSV is often a contributor to the BRD complex. Both individual and group antibiotic treatment may be indicated to mitigate the effects of the associated bacterial component.

**PARAINFLUENZA VIRUS (PI3)**

**Disease considerations:** Parainfluenza virus infections target the upper respiratory tract only, unlike IBR and BVD. Solitary PI3 infections are generally mild to moderate in appearance and most commonly due to failure of passive transfer of antibodies or decaying maternal antibodies. PI3 is more importantly noted as an initiator of secondary bacterial infections causing more severe disease.

■ **Vaccines**
  ● Killed
    □ Require two vaccinations 3 to 6 weeks apart, depending on the label.
    □ Labeled to be repeated after 5 or 6 months of age.
    □ Annual revaccination is recommended.
  ● Modified Live Parenteral
    □ Attenuated
    □ Immune response may be negatively impacted by presence of maternal antibody.
Usually labelled for single dose administration.
- No monovalent vaccine is currently available.
- Modified Live Intranasal
- Attenuated
- In combination with chemically altered temperature sensitive IBR and BRSV. Some combinations include non-temperature sensitive IBR.
- Labeled for use in 3-day old to 1-week old calves, depending on label.

For PI3 outbreak mitigation and vaccine strategies, see above for BRSV and IBR.

CLOSTRIDIAL DISEASES (C. HEMOLYTICUM AND TETANI NOT CONSIDERED CORE, BUT INCLUDED AS PART OF THE DISCUSSION ON RISK-BASED VACCINES)

Disease Considerations The organisms and associated clostridial diseases include:
- C. chauvoei  Blackleg
- C. septicum  Malignant Edema
- C. haemolyticum  Bacillary Hemoglobinuria
- C. novyi  Black Disease
- C. sordelli  Gas gangrene
- C. perfringens
types B, C, and D Enterotoxemia and enteritis
- C. tetani  Tetanus

Clostridial organisms are ubiquitous in the environment. Each Clostridium species has unique characteristics that require a practitioner to tailor a specific vaccination program to a particular set of circumstances.

Vaccines All clostridial vaccines are killed bacterin-toxoids with an adjuvant. The vaccines come in a variety of combinations designed to fit most production systems/disease situations.

These combinations include:
- 2-Way  Clostridium chauvoei, C. septicum
- 4-Way  Clostridium chauvoei, C. novyi, C. septicum, C. sordelli
- 7-Way  Clostridium chauvoei, C. novyi, C. perfringens Types B, C, D, Cl. septi-cum, C. sordelli
- 8-Way  Clostridium chauvoei, C. haemolyticum, C. novyi, C. perfringens Types B, C, D, C. septicum, C. sordelli or C. tetani
- 9-Way  Clostridium chauvoei, C. haemolyticum, C. novyi, C. perfringens Types B, C, D, Cl. septicum, C. sordelli, C. tetani

Additionally, there are:
- Monovalent Tetanus Bacterin Toxoids
- Enterotoxemia Toxoids
  - A
  - CD
  - BCD
- CD and Tetanus Toxoids

Vaccination Schedule Notes The vaccines come with a variety of labels with some common themes:
- The vaccines require boosting at well-defined intervals ranging from 3 weeks to 8 weeks initially to be effective.
- They are labeled to be boosted annually, or more frequently depending on disease frequency and unique farm challenges.
- Most labels indicate revaccinating after a certain age such as 4 months.
- All labels indicate to use the entire contents when opened.
- Anaphylaxis is identified as a risk factor when utilizing these vaccines.
- While clostridial vaccines are not Gram-negative, they should be carefully utilized in combination with Gram-negative antigens.
- It is up to the veterinarian to tailor the vaccination program to the disease challenge.
Outbreak Mitigation

Outbreak mitigation is situation dependent and may include:
- Revaccination
- Antibiotic therapy
- Treatment with anti-toxin

RISK-BASED VACCINATION

The following vaccines should be considered for inclusion in a vaccination program based on the risks and benefits of vaccination in a particular situation. The use of these risk-based vaccinations will vary dependent on geographical location, “closed” or “open” herd status and current or historic disease challenges within a particular group. Risk-based vaccinations could include:
- Coliform mastitis (considered core for dairy cows)
- *E. coli* for K99 strain diarrhea in calves
- *Salmonella* spp
- *Leptospira* spp (including Hardjo-bovis)
- Rotavirus
- Rabies virus
- *Brucella abortus*
- Coronavirus
- *C. haemolyticum*
- *C. tetani*
- *Mannheimia haemolytica, Pasteurella multocida, Histophilus somnii*
- *Moraxella bovis, Moraxella bovoculi*
- *Mycoplasma bovis*

COLIFORM MASTITIS VACCINATION

Vaccination of dairy cows and heifers for the prevention of disease from coliform mastitis is considered a core part of immunizations in this subset of the cattle industry. There are several approved vaccines for use in dairy cows, and they are based upon strains of modified Gram-negative bacteria with exposed antigens that are highly conserved across many Gram-negative organisms. While these vaccines do not prevent infections, they provide significant reductions in clinical signs during coliform mastitis.\(^\text{26}\)

Vaccination Schedule Notes

- Most of these vaccines indicate vaccination of dairy heifers at 7- and 8-months gestation.
- Mature cows should be vaccinated at dry-off, repeated 30 days later.
- Vaccination during lactation should be avoided with 45 days of parturition to avoid the immunosuppression and high energy demand of early lactation that can reduce vaccine efficacy.
- An approved vaccine is available for use in herds specifically with mastitis issues from *Klebsiella pneumoniae*, which is based on established SRP technology (see label directions for this vaccine schedule).
- Use of these vaccines in combination with other Gram-negative vaccinations may lead to increased risk of reactions and/or death.

**E. COLI VACCINATION FOR K-99 STRAIN DIARRHEA IN CALVES**

Vaccination for K-99 strain *E. coli* diarrhea, usually striking within the first week of life of the calf, can be provided by vaccinating the dam with several approved vaccines to be administered late in gestation for beef and dairy cows. Alternatively, or in conjunction with vaccination of the dam, *E. coli* antibodies can be delivered orally to the calf via bolus or gel at birth. Oral *E. coli* antibodies for calves are also a USDA-approved product. The utilization of these vaccines/antibodies in the face of disease challenges with K-99 *E. coli* diarrhea in calves can provide effective protection against disease.

Vaccination Schedule Notes

- Vaccination is indicated by the labels of these
vaccines late in gestation, with boosters administered 3 to 7 weeks prior to calving, depending on label.

- Annual revaccination is recommended 3 to 7 weeks prior to calving.
- Oral calf *E. coli* antibodies are labeled for administration within 12 hours of birth.
- *E. coli* vaccines are generally in combination with coronavirus, rotavirus and *Clostridium perfringens* Type C and D antigens.

## SALMONELLA SPECIES VACCINATION

*Salmonella* infections in beef and dairy herds can lead to serious and sustained issues of morbidity and mortality in cattle of all ages. The use of increased sanitation measures, testing, treatment, and culling can help reduce or eliminate *Salmonella*. The use of vaccination to prevent and/or eradicate *Salmonella* infections on beef and dairy farms has produced mixed results in the scientific literature, and the employment of these vaccines should be carefully considered by the bovine practitioner. A recent study indicated *Salmonella* vaccination of dry cows can lead cows to pass antibodies to calves via passive transfer but did not evaluate whether or not those antibodies provided protection from challenge.27 Another study demonstrated extra-label oral use of a *Salmonella* vaccine in dairy calves reduced mortality but did not affect rate of gain or pneumonia risk.28 While the literature has been equivocal in determination of efficacy of *Salmonella* vaccines, anecdotally in field settings, vaccines have helped reduce clinical signs and when used in combination with sanitation, testing and culling, may assist in the elimination of *Salmonella* from herds. The use of *Salmonella* vaccines to reduce and eliminate infections is also understandable given the multi-drug resistant strains present on some operations, and the food and human safety risks.

### Vaccination Schedule Notes

- There are several *Salmonella* vaccines approved and on the market.
- No vaccines are labeled for oral use in calves, so proceed with caution if considering the use of this route of administration.
- See labels for specific directions, but most vaccines are approved for cattle 2 weeks to 6 months of age and older. Booster in 2 to 4 weeks.
- Use of these vaccines in combination with other Gram-negative vaccinations may lead to increased risk of reactions and/or death.
- These vaccines consist of bacterins, modified live bacteria, or SRP technology.

## LEPTOSPIRA SPECIES VACCINATION

*Leptospira* species are among the most commonly implicated organisms in cases of reproductive loss in beef and dairy cattle in the North America.62,63 The types of *Leptospira* most frequently causing disease in cattle include *L. interrogans* Pomona, *L. borgpetersenii* Hardjo-bovis, *L. interrogans* Hardjo-prajitno, *L. interrogans* Canicola, *L. kirschneri* Grippotyphosa and *L. interrogans* Ictohaemorrhagiae, with Hardjo-bovis being the bovine-adapted strain. Several commercial vaccines are available as 5-way combinations of Pomona, Hardjo-prajitno, Canicola, Grippotyphosa and Ictohaemorrhagiae, as whole cell killed vaccines. One study indicated that heifers vaccinated with a pentavalent *Leptospira* vaccine that did not include Hardjo-bovis were protected from Hardjo-bovis infection and colonization.30 A 2018 meta-analysis of 1,237 articles indicated that vaccine efficacy to prevent *Leptospira* urinary shedding was 89.9%.31 A monovalent vaccine for Hardjo-bovis has been approved and is available for use individually, in addition to in combinations with the other five strains of *Leptospira* and MLV and killed
respiratory antigens. Vaccination for Hardjo-bovis can prevent colonization and significant urinary shedding by vaccinates.\textsuperscript{64}

While Hardjo-bovis has been associated with poor reproductive efficiency in cattle, vaccination with approved monovalent Hardjo-bovis vaccines has not improved fertility and calving rates in both beef and dairy cattle.\textsuperscript{32, 33}

**Vaccination Schedule Notes**
- As mentioned previously, there are several pentavalent Leptospira vaccines available, both alone and in combination with MLV or killed respiratory fractions. There is also a monovalent Hardjo-bovis vaccine, which is additionally available in combination with the pentavalent Leptospira vaccines and MLV or killed respiratory fractions.
- Most vaccines are labeled for an initial vaccination schedule of two doses 3 to 6 weeks apart, followed by annual revaccination.
- Use of these vaccines in combination with other gram-negative vaccinations may lead to increased risk of reactions and/or death.

**ROTAVIRUS VACCINATION**
Rotavirus is a common causal agent of diarrhea in neonatal calves. In addition to sanitation, vaccines targeted at pregnant cows and heifers to provide passive colostral rotavirus antibodies to calves at birth are commonly used. Research indicates that pregnant dams, when vaccinated with rotavirus vaccines, develop antibodies to rotavirus and pass these antibodies to their calves via colostrum, which protect the calf from disease due to experimental challenge.\textsuperscript{34,35,36} However, clinical trials demonstrating efficacy under current North American management conditions are lacking. These vaccines are killed virus, and are approved and available in multi-valent vaccines in combinations with E. coli, coronavirus and Clostridium perfringens Type C and D antigens. An oral/injectable modifiedlive combination is also available for oral use in newborns and as an injectable form for pregnant cows.

**Vaccination Schedule Notes**
- Administration of vaccine to pregnant cows is recommended in late gestation, with a booster administered 3 to 7 weeks later, ideally no later than 30 days before calving.
- Annual vaccination is recommended. See individual labels for directions.
- When using the oral attenuated vaccine in calves, vaccination is recommended prior to 24 hours of age.

**RABIES VACCINATION**
Rabies vaccination in cattle is an uncommon practice compared to companion animals and in the equine industry. Use of rabies vaccine in cattle should be considered in areas of high risk (i.e., in a locality or property with a known/active outbreak), and in cattle with frequent contact with humans such as show cattle and petting zoo exhibits. There are currently four killed virus rabies vaccines licensed for use in cattle in the U.S. Research data indicates booster vaccines, administered up to one year after the primary dose, provide a significant anamnestic response.\textsuperscript{37} Two doses of the vaccine are recommended to achieve a protective antibody level.\textsuperscript{37}

**Vaccination Schedule Notes**
- As mentioned above, these are killed virus vaccines.
- Labels indicate vaccinations can begin as young as 3 months of age.
- Boosters should be administered at 1 year of age.
- When vaccinating calves nursing rabies-vaccinated cows, vaccination should be delayed until 5 to 6 months of age.\textsuperscript{37}
**BRUCELLA ABORTUS VACCINATION**

Vaccination of cattle in the U.S. for *Brucella abortus* has been one of the most successful disease interventions in the cattle industry. All 50 states are considered “Free” of *Brucella abortus* by USDA APHIS. Vaccination for *B. abortus* is not required by the USDA, but is instead left up to each state to decide. It is recommended that the states surrounding the Yellowstone National Park area vaccinate, due to *Brucella* presence in wildlife in the park. The RB51 vaccine is the only licensed *B. abortus* vaccine on the market and is a modified-live rough mutant strain. This vaccine has been proven effective in prevention of infection and abortion in cattle by *B. abortus* in a high-prevalence herd.38 RB51 vaccination does not protect cattle from *Brucella suis* infection.39 The vaccine is licensed for female cattle aged 4 to 12 months, but individual states may narrow this eligible age range for beef and dairy heifers.

Vaccination of adult cattle is only permitted via approval and guidance by state and federal animal health officials. All cattle vaccinated with the RB51 vaccine as part of the official calfhood vaccination program must identify the animal with an official USDA vaccination ear tag, in addition to placing a vaccination tattoo in the right ear of the animal. All cattle vaccinated are required to have their information (ID, age, breed, sex, etc.) recorded onto form VS4-26 and sent to state animal health officials for record keeping.

**Vaccination Schedule Notes**

- The vaccine is licensed for female cattle aged 4 to 12 months, but consult your state guidelines as they may narrow this requirement.
- This vaccine may only be given by a federally accredited veterinarian or a state or federal animal health official.
- Some states require cattle to be *Brucella* vaccinates prior to entry.
- Vaccination for *Brucella* can be an added benefit when planning to market cattle across state lines, as the mandatory USDA ID requirement for interstate movement has already been completed as part of the vaccination process.
- The use of RB51 vaccines in dairy herds selling raw milk should be evaluated carefully, as human infections with RB51 *Brucella* after drinking the raw milk of vaccinates have been reported.40

**CORONAVIRUS VACCINATION**

Bovine coronavirus infections cause gastrointestinal and respiratory disease in both neonatal, growing and mature beef and dairy cattle. It is estimated by seroprevalence studies that over 90% of cattle are exposed to bovine coronavirus at some point in their life.41 Coronavirus infections in cattle cause three different disease manifestations, consisting of malabsorptive diarrhea in neonatal calves, winter dysentery in adult cows, and respiratory disease in calves and feedlot cattle. Cattle infected with coronavirus shed virus particles in both their feces and nasal secretions.41 Virus shedding can be detected in both clinically ill animals and apparently healthy individuals.41 Bovine coronavirus has been implicated as a contributor to the BRD complex and the resultant pathology can vary dependent on the strain of coronavirus, in addition to age, co-infections with other respiratory agents, weather...
There are several approved bovine coronavirus vaccines available, all of which are modified-live. These range in application from intra-nasal applications for mucosal immunity to injectable parenteral vaccines to be delivered to the calf or pregnant dam. While there is much observational and anecdotal data supporting the use of coronavirus vaccination for the prevention of respiratory and enteric disease, current studies only examine vaccine safety and generation of the immune response, and do not measure if these vaccines are efficacious against disease. While it is evident in the current literature that these vaccines are immunogenic, it is up to the individual practitioner to determine if vaccination can benefit a particular herd.

**Vaccination Schedule Notes**
- Available vaccines are modified-live or killed virus.
- An intranasal product is on the market and can be applied to calves as young as 1 day of age.
- An oral/IM formulation is also available for newborn calves and pregnant cows, respectively. Calves can be vaccinated at birth orally with this product. Adult cows should be vaccinated twice in late pregnancy, with the second dose given at least 30 days prior to calving.
- Coronavirus vaccines are also available in combination with *E. coli*, rotavirus and *Clostridium perfringens* Type C and D. These products should also be given in twice in late pregnancy, per label directions.

**CLOSTRIDIUM HAEMOLYTICUM VACCINATION**
*Clostridium haemolyticum*, like the other clostridial organisms listed in the core discussion in this document, is a Gram-positive spore-forming bacteria that is often found in the soil and also in the internal organs of apparently healthy cattle. This organism may also be referred to as *Clostridium novyi* type D. *C. haemolyticum* causes a disease known as bacillary hemoglobinuria (Red Water), most commonly due to liver fluke migrations, liver abscesses, septicemia and other conditions leading to a low-oxygen environment in the liver. Given the association of liver fluke migrations and this disease syndrome, bacillary hemoglobinuria is more prominent in some geographic locations, especially low-lying swampy areas. Practitioners should evaluate the risk of fluke infection and other risk factors prior to vaccination for *C. haemolyticum*.

**Vaccination Schedule Notes**
- Vaccination for *C. haemolyticum* can be achieved via several approved vaccines that are killed bacterin-toxoids, like other clostridial antigens.
- This agent is supplied in combination with several other clostridial killed bacterin-toxins, there are no monovalent vaccines.
- Vaccination can be given at any age, per label, and should be readministered 4 to 6 weeks later.
- Revaccination is recommended every 6 months.

**CLOSTRIDIUM TETANI VACCINATION**
*Clostridium tetani* is another Gram-positive spore forming bacteria that is ubiquitous in the environment, and an ever-present risk for disease in low-oxygen environments such as contaminated wounds, surgical areas (i.e., castration sites) and during metritis. Cattle are generally assumed to be at lower risk for development of tetanus compared to other farm animals (especially horses), and thus are not routinely vaccinated for tetanus. Additionally, most multivalent clostridial vaccines do not contain *C. tetani* antigens. Vaccination for
tetanus should be considered standard of care by the practitioner in situations where cattle are being banded for castration or tail docking purposes, or in other clinical scenarios where a low-oxygen environment might be created from a surgical procedure or wound. Vaccination should also be strongly considered on cattle operations with a history of tetanus cases.

Vaccination Schedule Notes

- Vaccination for tetanus does not provide immediate protection from C. tetani toxins, thus simultaneous vaccination at the time of tail docking or castration with bands may not provide adequate protection from clinical signs and death. Vaccination should occur at least 3 weeks prior to the surgical event to allow enough time for the development of antibodies, and ideally after the secondary booster dose for maximum protection.
- There are few data to support the co-administration of tetanus antitoxin and tetanus toxoids at the time of castration. The only data found for this practice refers to horses and demonstrated that antitoxin and toxoid co-administration did not lead to interference in natural antibody production post-vaccination.47 This reference also advised against mixing antitoxin and toxoids in the same syringe and suggested placing these products far apart during injection to avoid potential local interference of the antitoxin with the vaccine.47
- Tetanus vaccine is supplied as a killed bacterin-toxoid, either as a monovalent vaccine, or in combination with other clostridial toxoids, or Clostridium perfringens Type C and D antitoxins.
- Most vaccines indicate a booster vaccination 4 to 6 weeks after initial dose, and annual revaccination.

MANNHEIMIA HAEMOLYTICA, PASTEURELLA MULTOCIDA AND HISTOPHILUS SOMNI VACCINATION

The published evidence for use of toxoids or killed bacterin-toxoids for prevention of respiratory disease due to M. haemolytica, P. multocida or H. somni is mixed. A meta-analysis conducted in 2012 by Larson and Step indicated no evidence of benefit resulting from vaccination against H. somni for mitigating the incidence and effect of the BRD complex.48 No trials were found that evaluated P. multocida vaccines in isolation. This meta-analysis indicated that M. haemolytica vaccines (tested in 15 trials), and M. haemolytica-P. multocida combination vaccines (tested in three trials), significantly decreased BRD morbidity in feedlot cattle. However, because there was lack of consistency in the direction and magnitude of efficacy, the degree of benefit was small.48 The difficulty in evaluating vaccination against these three agents is related to variability in the types and designs of studies conducted. Vaccination with these antigens is certainly immunogenic, and can provide protection against experimental challenge, as many studies have indicated. However, the protection against disease in the field as measured by controlled clinical trials is not consistent. One study evaluating the use of modified live M. haemolytica and P. multocida vaccines in dairy calves reported no difference in treatment outcomes.49

Veterinarians utilizing these products should carefully evaluate the present evidence in the literature not only for their immunogenicity, but also protection against disease. When incorporating these antigens into vaccination protocols veterinarians should also consider that these are Gram-negative organisms that may cause increased risk of adverse reactions, especially when added to protocols containing other Gram-negative antigens.
■ Vaccination Schedule Notes
● The majority of commercial vaccines for these three antigens are toxoids or killed bacterin-toxoids, available combined with other viral respiratory fractions, or as monovalent vaccines.
● *P. multocida* and *M. haemolytica* are also available in combination as an avirulent live culture for parenteral or intranasal administration.
● These vaccines, both killed fractions and avirulent live culture, generally recommend a single dose for initial vaccination, followed by annual revaccination.

**MORAXELLA BOVIS AND MORAXELLA BOVOCULI VACCINATION**

Vaccination for infectious bovine keratoconjunctivitis (IBK or pinkeye) has historically focused on the main bacterium implicated in IBK, *Moraxella bovis*. There are many approved vaccines on the market for *M. bovis*, which consist of bacterins mostly in liquid injectable form, but also in a pellet format. Despite the many available biologic products for this organism, and the fact that licensed vaccines must show benefit in experimental challenge studies, the efficacy of *M. bovis* vaccination to prevent IBK in the field is not supported by published controlled clinical trials.\(^5^1,\)^\(^5^2,\)^\(^5^4,\)^\(^5^5\) The discovery of the presence of another organism implicated in IBK infections in cattle, *Moraxella bovoculi*, has led to further development of a conditionally licensed vaccine for this organism. A randomized blinded challenge study did not support a causal role for *M. bovoculi* in IBK, while a role for *M. bovis* was supported.\(^5^3\) A single conditionally licensed vaccine for *M. bovoculi* is available, however its efficacy is also not supported in the current literature.\(^5^0\) With the discovery of multiple agents implicated in IBK in cattle, and the demonstrated lack of efficacy of *M. bovis* vaccines (and also *M. bovoculi*), the use of autogenous vaccination with *M. bovis* and *M. bovoculi* has become quite popular in bovine medicine. Despite this popularity, recent published data do not support efficacy of autogenous vaccines.\(^5^6,\)^\(^5^7\) It is likely that multiple virulence factors, a complex of organisms and animal/environmental conditions, and wide antigenic variability lead to lack of success of IBK vaccines in randomized controlled trials. If bovine veterinarians are considering vaccination for IBK, whether using approved products or autogenous vaccines, they should carefully weigh the literature, cost of implementation, and possible side effects of an additional Gram-negative organism into their vaccine protocols.

■ Vaccination Schedule Notes
● There are many approved products on the market for IBK, mainly consisting of bacterins, but also subunit vaccines based on pili.
● *M. bovis* vaccines are available as monovalent vaccines, and also in combination with clostridial agents.
● Most labels indicate a primary vaccination, with a secondary booster 3 to 4 weeks later. The conditionally licensed *M. bovoculi* vaccine indicates vaccination beginning at 14 weeks of age and booster at 3 weeks.
● As with several other vaccines mentioned in this document, care should be given when administering this vaccine with other Gram-negative agents.

**MYCOPLASMA BOVIS VACCINATION**

*Mycoplasma bovis* is part of the BRD complex and is a source of significant morbidity and mortality in cattle from respiratory disease, in addition to mastitis and arthritis. There are several *M. bovis* bacterins approved for use in cattle, however their efficacy has not been supported by published con-
trolled field trials in dairy calves.\textsuperscript{58,59} Published controlled field trials of *Mycoplasma bovis* vaccines in stocker or feedlot cattle are lacking. In experimental challenge situations, *Mycoplasma bovis* vaccines have looked quite promising, but when extended to field trial situations, efficacy is not achieved.\textsuperscript{58} In some instances, vaccinates in clinical trials have experienced more severe disease than non-vaccinated controls.\textsuperscript{60, 61} In addition to commercially licensed vaccines, autogenous *Mycoplasma bovis* vaccines have also been utilized by bovine practitioners, but evidence of their efficacy is scant. Because of this lack of evidence for efficacy, and possibility of vaccine-enhanced disease, practitioners should evaluate husbandry and management changes prior to consideration of *Mycoplasma bovis* vaccines in the farm setting.

\begin{itemize}
  \item **Vaccination Schedule Notes**
  \begin{itemize}
    \item The available licensed vaccines for *Mycoplasma bovis* are killed bacterins.
    \item Both single dose administration and a boosted vaccine series are recommended with the approved vaccines, depending on the label.
  \end{itemize}
\end{itemize}

**BOVINE VACCINATION PROTOCOLS**

When designing protocols to fit various production systems in the cattle industry, whether it is dairy, beef cow-calf or stocker/feedlot, it is important to take into consideration age, nutrition status, previous vaccination history, pending transport, weaning, environmental challenges, and other important factors. One vaccination protocol will not fit into all operations and given the wide range of cattle production systems, it is difficult to standardize one particular vaccine regimen over another. The AABP considers the following antigens “core” to bovine vaccination, suggesting they are likely beneficial to most cattle: IBR, BRSV, BVD, PI3 and combination vaccines against *C. perfringens*, *C. novyi*, *C. sordelli*, *C. septicum* and *C. chauvoei*. Beyond these core vaccines, the practitioner must weigh risks and benefits specific to the cattle in question to determine if additions to the vaccine regimen are warranted. An excellent starting point for creation of vaccination protocols for cattle can be found here: *Practical Immunology and Beef and Dairy Vaccination Protocols: Starting from Ground Zero—What, When and How*, by Dr. Chris Chase, 2020 AABP Recent Graduate Conference Proceedings.

**SUMMARY**

The Vaccination Guidelines in this document are a starting point for bovine practitioners developing vaccination protocols for use in their clients’ operations. This includes a summary of types of vaccines, vaccine safety and reporting mechanisms, suggested core vaccinations, risk-based vaccination, adverse reactions and general use recommendations. Creation of protocols takes an understanding of the science of vaccination and the immune response, disease threats, interpretation of the scientific literature and the ability to implement protocols for clients with varying production systems and needs. The discussion of risk-based vaccines, along with expanded literature references, are intended to assist the practitioner deciding whether or not to include such vaccines in certain protocols. The writing of these Guidelines has highlighted the need for further research on vaccines for multiple diseases of cattle, including basic scientific research on vaccine platforms, safety, and controlled field trials to assist in the evaluation of efficacy and efficiency on the farm. The issue of antimicrobial use in cattle, and subsequent risks for antimicrobial resistance development, compound the need for more investigation into the use of biologics for disease control and prevention in cattle.
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