KEY ELEMENTS FOR IMPLEMENTING ANTIMICROBIAL STEWARDSHIP PLANS IN BOVINE VETERINARY PRACTICES WORKING WITH BEEF AND DAIRY OPERATIONS

AABP ANTIMICROBIAL STEWARDSHIP GUIDELINES

The goal of this document is to provide bovine veterinarians with best practices for designing, implementing, and monitoring antimicrobial stewardship programs with their clients. These best practices are aimed at veterinarians that administer antimicrobials, are responsible for oversight of drug use or treatment protocols, or who make recommendations for use of antimicrobials.

The focus is on best practices for veterinarians with defined and defensible Veterinarian-Client-Patient Relationships (VCPR) or who are Veterinarians of Record. Elements may be applicable to veterinarians with other relationships to clients and patients.

DEFINITION OF ANTIMICROBIAL STEWARDSHIP

Antimicrobial stewardship is the commitment to reducing the need for antimicrobial drugs by preventing infectious disease in cattle, and when antimicrobial drugs are needed, a commitment that antimicrobials are used appropriately to optimize health and minimize selection for antimicrobial resistance.

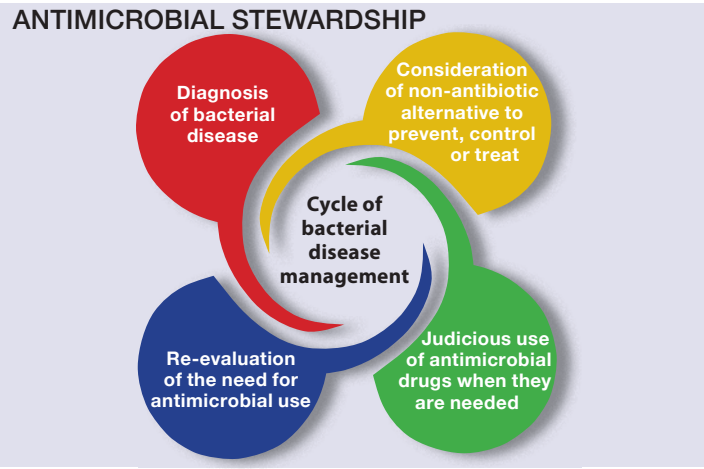
KEY ELEMENT 1: LEADERSHIP COMMITMENT

Commitment to leadership in antimicrobial stewardship in bovine practice means being responsible for the entire cycle associated with bacterial disease management. It includes accepting responsibility and accountability for antimicrobial prescribing, dispensing, and administration. This commitment also includes identifying leaders within the practice and client operations to share in antimicrobial stewardship.

Multi-veterinarian practices may find it beneficial to designate one main leader to coordinate efforts and bring information and opportunities to their colleagues. Everyone in the practice should shoulder leadership responsibility including involvement of other stakeholders such as veterinary technicians, cattle operation managers, nutritionists, farm employees, drug distributors, animal health companies, pharmacies, and contract service providers such as hoof trimmers, in all settings in which antimicrobial drugs are used.

VETERINARIANS CAN BE LEADERS IN ANTIMICROBIAL STEWARDSHIP BY ASKING THE FOLLOWING QUESTIONS:

- Have I made a commitment to apply what I learn from continuing education and to relay what I learn to my clients and colleagues?
- Have I provided the necessary training and education about the need for antimicrobial stewardship and ways to use antimicrobial drugs judiciously for on-farm personnel, if appropriate/necessary?
- Have I made the commitment to use what I learn from each of these therapeutic events and investigations to further the training and education of all stakeholders?
- Have I considered whether my personal economic gain has influenced my decisions to treat, dispense, or prescribe an antimicrobial drug?



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ONCE A NEED FOR ANTIMICROBIAL DRUGS HAS BEEN IDENTIFIED, JUDICIOUS USE INCLUDES CONSIDERATION OF THE FOLLOWING:

- Have I identified the organ system(s) affected and the most common infectious agent(s) to make an informed selection of an appropriate regimen including antibiotic, dose, and route of administration?
- Is the regimen safe?
- Am I committed to complete the cycle of disease management by following the judicious use of antimicrobial drugs with reevaluation of their need?
- Am I committed to using antimicrobial drugs in a manner that does not increase short-term benefits at the expense of long-term loss of antimicrobial susceptibility and effectiveness?
- Do I have a veterinary-client-patient-relationship?
- Have I followed the legal requirements for using antimicrobial drugs by selecting approved products when available or choosing legally acceptable extra-label use?
- Have I avoided causing a violative residue?

KEY ELEMENT 2: DRUG EXPERTISE

It is the responsibility of the veterinarian to continuously seek new information about the use of antimicrobial drugs. This may take the form of consulting infectious disease specialists, attending professional continuing education opportunities, searching for and reading peer-reviewed published research, or reviewing rigorously conducted knowledge summaries. Knowledge summaries may include online decision-support tools, systematic reviews and meta-analyses, or critically appraised summaries of published data.

Veterinary educators are called to include education about all aspects of antimicrobial stewardship so that new veterinary graduates and those in animal science and related disciplines have the knowledge and skills necessary to be good stewards.

Bovine practitioners should provide antimicrobial use protocols and treatment guidelines specific for each operation as described in the AABP Guideline “Establishing and maintaining the veterinarian-client-patient relationship in bovine practice” and “Drug use guidelines for bovine practice.” Well-designed protocols make all the steps in antimicrobial decision-making transparent, and provide a tool for accountability and tracking.

KEY ELEMENT 3: TRACKING ANTIMICROBIAL DRUG USE

Bovine practitioners should periodically review treatment records, drugs present on the farm in relation to treatment protocols, and on-farm antimicrobial drug dispensing and usage. This requires appropriate record systems.

Tracking may include monitoring the pathogens associated with clinical disease, including antimicrobial susceptibility patterns, or evaluating treatment outcomes such as retreatment, culling, and case fatality rates. Knowledge of these parameters on a herd basis can help guide further investigation and changes in treatment protocols.

Actual antimicrobial use in treatment records should be compared to protocols for indications of protocol drift. Deviations from protocol should be addressed through training and other corrective actions as appropriate.

KEY ELEMENT 4: REPORTING

Bovine practitioners should support efforts to report antimicrobial drug use across farms in order to benchmark and compare usage, while maintaining client confidentiality.

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KEY ELEMENT 5: ACTION

Stewardship programs require action in addition to monitoring and tracking. Stewardship leader(s) should review activities and recommend appropriate actions on a regular basis. Below are some examples of ways to take action.

- Review the disease prevention programs such as vaccination, nutrition, and environmental management programs for specific disease conditions to assure optimal husbandry and management are being employed. Specific examples include:
  - Examine processing and arrival programs in the feedlot.
  - Review pre-weaned dairy calf management to reduce scours and respiratory disease and need for treatment.
  - Examine treatment records to estimate the percentage of entries for a single disease challenge (e.g., mastitis on a dairy, bovine respiratory disease complex on a feedlot). Make a plan with the owner or manager to reduce the incidence of disease and review records again in 6 months.
- Review diagnosis/treatment protocols developed for different disease syndromes.
  - Are the protocols up to date for the applicable disease challenges with regard to indication for use, dosage, route, and duration?
  - Examine treatment records to estimate the percentage of entries that include all of the necessary recorded items such as: antimicrobial drugs used, indication for use, and regimen (dose, route, duration, and frequency). Make a plan with the owner or manager to increase this percentage of complete records by a particular percent and review again in 6 months.
  - Look at the client's drug inventory and purchasing as a measure of protocol compliance.
- Review the published evidence for efficacy of specific antimicrobials for pathogens seen in the practice.
  - Pick one or more high prevalence diseases in a production class and create a progress plan for:
- Herd management changes that have the potential to reduce disease pressure and prevalence over the subsequent period.
- A review of current treatment protocols for that disease and suggestion of refinements in terms of a decision tree for when and how to treat.
- Providing for reliable treatment and outcome records for later review.
  - Establish a schedule (annual, semiannual, quarterly) to review disease rates, treatment frequency, and changes in treatment outcome quality parameters.
  - Commit to seeking/creating a learning system around a selected disease such that repetition of the status quo is an unlikely long term outcome. Identify and review the disease, diagnosis, treatment and outcome with all team members.
  - Be able to measure, identify and describe the benefits of improvements garnered from these efforts.

RESOURCES

- *Evidence Based Veterinary Medicine Association* www.ebvma.org
- *Food Armor®* www.foodarmor.org
- *AABP Guidelines for Establishing and Maintaining The Veterinarian-Client-Patient-Relationship in Bovine Practice* http://www.aabp.org/resources/aabp_guidelines/vcprguidelinefinal11-2013.2.pdf
- *AABP Prudent Antimicrobial Use Guidelines for Cattle* http://www.aabp.org/resources/aabp_guidelines/AABP_Prudent_Antimicrobial_Use_Guidelines-2013.pdf
- *AABP Drug Use Guidelines for Cattle Practice* http://www.aabp.org/resources/aabp_guidelines/druguseguidelines_2015-4-8-1.pdf
- *FDA Guidance for Industry #152 Appendix A: Ranking of Antimicrobial Drugs According to their Importance in Human Medicine, pg 28* https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf
- *FDA Guidance for Industry #213* https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf
- *FDA Guidance for Industry #209 The Judicious Use of Medially Important Antimicrobial Drugs in Food-Producing Animals* https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf

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CASTRATION GUIDELINES

These guidelines from the American Association of Bovine Practitioners serve to assist veterinarians with enhancing the welfare of their clients' cattle by providing guidance related to castration of calves on beef and dairy operations. Essential to this process is that consultation occur between the Veterinarian of Record and the client to develop operation-specific castration protocols that consider age of castration, castration technique, pain mitigation strategies and appropriate recordkeeping for the use of extralabel drugs. Adequate education and training should be provided so that the producer and any caretakers are comfortable and competent, particularly if they are involved in the procedure. The use of written, herd-specific protocols to document these discussions is encouraged. Protocols should be reviewed and modified as needed on a regular basis. Training and education should also be consistently reviewed and updated or revisited when appropriate.

Regardless of age or castration method, castration is understood to be a painful procedure. In the North American beef industry, the benefits of castration typically outweigh the potential negative implications, particularly when care is taken to appropriately mitigate pain and decrease stress through timely age selection, competent castration technique, proper handling, and adequate facilities. Castration lowers testosterone levels, typically resulting in reduced aggressiveness toward other animals and humans, decreased sexual activity/behavior, and improvements in both carcass characteristics and overall quality grade.

AGE

Performing castration at the earliest age possible reduces both stress and pain associated with the procedure and decreases healing time. It may also result in less risk of injury to the personnel involved with the castration procedure(s). Castration prior to three months of age is encouraged or at the first practical opportunity after three months of age.[1] This age will vary between production systems and should be based on recommendations of the Veterinarian of Record and discussions with farm/ranch management. Castration should not be delayed for the purpose of enhancing growth as there are no proven growth benefits associated with this practice.[2,3]

RESTRAINT

Calves should be restrained for castration in a way that minimizes stress and the risk of injury to the animal and the operator. The use of a squeeze chute, tilt table, calf cart, lariat or halter are examples of tools that may be used to achieve this goal. Facilities specifically designed for proper cattle handling should be used to ensure employee safety and calm and effective cattle handling. Chemical restraint may be included in the procedure to further minimize stress to the animal as well as the humans involved. Personnel involved with cattle handling should be trained appropriately and be provided the time and resources necessary to achieve low-stress handling.

METHOD

Surgical removal of the testicles or the use of a rubber ring are the preferred methods of castration. The most appropriate method should be determined by the Veterinarian of Record in consultation with farm/ranch management based on the best interest of the health and well-being of the animal within the environment in which it is

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being raised. Both methods result in acute and chronic pain, which should be mitigated in the most appropriate and practical ways possible. Additionally, administration of tetanus prophylaxis and/or antitoxin should be considered the standard of care for banding.

PAIN MANAGEMENT

All methods of castration cause pain. The AABP recommends that pain management be considered the standard of care during all castration procedures. It is critical that producers work with their Veterinarian of Record to develop the most appropriate, individualized pain management protocol for their operation. Beyond the critical benefits to animal welfare, scientific evidence supports castration pain management's positive impact on average daily gain and feed intake. There are currently no approved drugs in the United States for use in cattle with an indication to provide analgesia associated with castration pain. Animal Medicinal Drug Use Clarification Act (AMDUCA) regulations allow extralabel drug use provided a valid veterinarian-client-patient relationship (VCPR) exists and the drug selection process, records and withholding times outlined in the AMDUCA regulations are followed.

LOCAL ANESTHESIA Use of a local anesthetic immediately prior to castration mitigates the acute pain associated with the procedure and provides up to five hours of post-procedural analgesia. Testicular blocks, spermatic cord blocks, and epidurals can minimize pain associated with castration. The use of sedatives prior to administration of local anesthetics can make the procedure safer and less stressful. The use of local anesthetics and sedatives requires a prescription and should be administered in the context of a valid VCPR. It is critical that adequate records are kept regarding the extralabel use of drugs and that farm/ranch personnel are educated about potential risks or hazards associated with specific medications.

SYSTEMIC PAIN RELIEF Systemic pain relief should be used to provide additional and longer lasting pain relief. Systemic pain mitigation protocols may include opioids, alpha 2 agonists, gabapentin and non-steroidal anti-inflammatory drugs (NSAIDS). These medications may be used alone or in combination to effectively mitigate post-procedural pain associated with castration. Meloxicam has been shown to mitigate post-castration procedure pain for up to 48 hours following a single dose of the drug,[4] which promotes improved short-term weight gain and feed intake compared to calves that were not administered meloxicam.[1] The use of NSAIDs for pain mitigation following castration in calves older than seven days of age has been shown to reduce the risk of bovine respiratory disease.[5] Topical NSAID applications make the administration of NSAID therapy at the time of castration practical in most instances when oral or injectable administration is not possible. Additional doses during the healing process should be considered where practical and are encouraged especially when the procedures are delayed beyond three months of age.

For a list of references regarding castration pain management, see Castration Pain Management References at https://aabp.org/committees/resources/Castration_References_2024.xlsx.

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DEFINITIONS

ANALGESIA Alleviation of pain, patient is alert.[6]
ANESTHESIA Without sensation, patient is asleep and cannot be awakened, amnesia and loss of reflexes.[6]
SEDATION Slight depression, patient is awake.[6]

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DEHORNING GUIDELINES

Dehorning cattle reduces the risk of injury to the animal, other cattle and people and, during transportation to slaughter facilities, reduces bruising of carcasses. This guideline from the American Association of Bovine Practitioners (AABP) serves to assist veterinarians and producers with enhancing the welfare of their client's cattle by providing guidance related to dehorning of calves on beef and dairy operations. Essential to this process is that consultation occur between the Veterinarian of Record and the client regarding age at dehorning, dehorning techniques, and pain mitigation strategies that are appropriate for each operation. The use of written, herd-specific protocols to document these discussions is encouraged. Such protocols should be reviewed on a regular basis.

AGE

Ideally, dehorning is completed when the calf is young and should be performed at the youngest age possible. Disbudding, which involves the removal or destruction of the horn-producing corium in young calves, is preferred over dehorning if it can be performed within the management system. Disbudding is achievable prior to two weeks of age and may be performed as early as the first 24 hours of life. Dehorning is considered a more painful procedure with longer healing time, as the horns are removed after the horn-producing corium has attached to the skull. In dairy operations where calves are handled daily, disbudding or dehorning should be performed by 8 weeks of age. In open range beef operations, dehorning should be performed as early as the management system allows. Accomplishing dehorning prior to 3 months of age or the first practical opportunity after 3 months of age is encouraged. This age will vary between production systems and should be based on recommendations of the Veterinarian of Record and discussions with farm/ranch management. The added stress that occurs with increased age at dehorning should be considered. It is critical that producers work with their Veterinarian of Record to ensure appropriate procedures are in place to promote healing and minimize pain.

RESTRAINT

Calves should be restrained for dehorning in a way that minimizes stress and the risk of injury to the animal and the operator. Chemical restraint (sedation) may be used to minimize stress and increase ease of handling. It is important to note that some sedatives do not have analgesic properties and the use of sedation may not eliminate the need for other pain management strategies. Federal law restricts sedatives to use by or on the order of a licensed veterinarian. Employees should be trained on safe, low stress handling and be provided the time and resources necessary to achieve this type of handling. The use of a squeeze chute, tilt table, calf cart or halter may accomplish proper head restraint. The application of local anesthetics to minimize the need for excessive restraint should be utilized.

METHOD

The Veterinarian of Record should work with the producer to develop written protocols for disbudding or dehorning that work best within their farm management system. Acceptable methods for disbudding include application of caustic paste or an electric/gas iron to destroy the horn producing corium. The use of caustic paste is less effective and discouraged after the calf is 2 weeks of age and ideally should be applied within the first few days of life. Detailed instructions for the application are available.[1]

Larger horns may require mechanical removal. A protocol should be in place for managing wounds that are the result of using mechanical dehorning devices, which would include control of infection, pain and fly control. Dehorning at the earliest age possible within the management system mitigates the need for gouge dehorning

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in most circumstances. The use of elastic banders in animals with well-developed horns is not recommended due to increased rates of failure, increased pain and delayed healing.[2]

Producers of breeds with access to polled sires should be encouraged to incorporate polled genetics into their herds, as genomics and selection make this a viable option for the future with many dairy breeds. The National Animal Health Monitoring (NAHMS) Beef 2017 Cow-Calf Study reports that only 7.8% of beef cattle in the US are horned, improved from 27.8% horned in 1997 and 12.4% in the 2007-2008 survey

PAIN MANAGEMENT

All methods of disbudding and dehorning cause pain. AABP recommends that pain management be considered the standard of care during all dehorning and disbudding procedures. Producers are encouraged to work with their Veterinarian of Record, who is best able to develop the most appropriate, individualized pain management protocol for their operation. Scientific evidence supports that it is possible to enhance animal welfare associated with these necessary procedures with the implementation of pain management protocols.

Local Anesthesia

Use of a local anesthetic mitigates the immediate pain associated with disbudding and dehorning and provides up to five hours of post-procedural analgesia. There are a variety of local anesthetic techniques including a cornual nerve block or horn bud infiltration. The local anesthetic protocol should be determined and prescribed by the Veterinarian of Record. Federal law restricts the use of local anesthetics to use by or on the order of a licensed veterinarian.

Systemic Pain Relief

The use of non-steroidal anti-inflammatory drugs (NSAIDs) should be used to provide additional and longer lasting pain relief. The use of injectable, topical or oral NSAIDs are acceptable for pain mitigation in the immediate post-operative period. Meloxicam has been shown to mitigate post-procedure pain for up to 48 hours after a single dose of the drug.[3] Topical NSAID applications make the administration of NSAID therapy at the time of disbudding or dehorning practical in most instances when oral, IV or IM administration is difficult although further study is warranted to determine its effectiveness in mitigating dehorning pain.[4] The type of NSAID used should be prescribed by the Veterinarian of Record. There are currently no approved drugs in the United States for use in cattle with an indication to provide analgesia associated with dehorning pain. AMDUCA regulations allow extra-label drug use provided a valid Veterinarian-Client-Patient Relationship exists and the drug selection process, records and withholding times outlined in the AMDUCA regulations are followed.

DEFINITIONS

- *Analgesia: Alleviation of pain, patient is alert.*[5]
- *Anesthesia: Without sensation, patient is asleep and cannot be awakened, amnesia, and loss of reflexes.*[5]
- *Dehorning: Removal of the horns and horn-producing corium after the horns have formed and are attached to the skull.*[6]
- *Disbudding: Removal or destruction of the horn producing corium in young calves. At this age the horn buds are free-floating and not attached to the skull.*[6]
- *Sedation: Slight depression, patient is awake.*[5]

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GUIDELINES FOR THE HUMANE EUTHANASIA OF CATTLE

OVERVIEW

Livestock caretakers have an obligation to ensure the welfare of animals under their care. Euthanasia of an animal suffering from irreversible disease or injury is a primary responsibility of the caretakers. Euthanasia is defined in the "AVMA Guidelines for the Euthanasia of Animals (2020)" as: "ending the life of an individual animal in a way that minimizes or eliminates pain and distress." When properly conducted, euthanasia results in a rapid loss of consciousness followed by cardiac and respiratory arrest and death. The contents of this pamphlet are intended to aid animal caretakers and owners, livestock market operators, animal transporters, and veterinarians in choosing effective euthanasia methods.

The "AVMA Guidelines for the Euthanasia of Animals (2020)" recognizes and accepts three primary methods of euthanasia for cattle:

- **Intravenous** (IV) administration of a lethal dose of a barbiturate or barbituric acid derivative to induce a transition from consciousness to unconsciousness and death.
- **Gunshot** using an appropriate firearm, ammunition and anatomic site to cause physical disruption of brain activity by direct destruction of brain tissue.
- **Penetrating captive bolt** to induce unconsciousness in combination with an adjunctive step such as exsanguination, intravenous administration of a solution of either potassium chloride or magnesium sulfate, or pithing (increasing destruction of brain and spinal cord tissue) to ensure death. Non-penetrating captive bolt can be used for the euthanasia of neonates and calves less than two to three months of age when followed by use of an adjunctive method to assure death.

When properly applied, the above euthanasia methods cause the animal's rapid loss of consciousness and death without undue distress to the animal.

INDICATIONS FOR EUTHANASIA

The following lists contain examples of conditions or situations of compromised cattle for which prompt euthanasia is generally indicated (Shearer 2008, Shearer 2018, Griffin 2015):

Indications for prompt euthanasia

- Fracture, trauma or disease of the bony or soft tissue structures resulting in immobility or inability to stand
- Disease conditions for which no effective treatment is known (i.e., Johne's disease, lymphoma)

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- Diseases that involve a significant threat to human health (i.e., rabies)
- Disease conditions for which treatment will not be pursued due to cost
- Diseases for which the level of care to properly manage pain and distress and treat the disease is beyond the willingness or ability of the farm or facility
- Emaciation and/or debilitation from disease, age or injury resulting in an animal being too compromised to be slaughtered on site, transported, or marketed
- Advanced neoplastic conditions (e.g. cancer eye, lymphoma)
- Congenital or acquired conditions that produce a level of pain and distress that cannot be managed adequately by medical or management methods
- Nonambulatory cattle with signs of uncontrolled pain or distress. (Stull 2007)

Euthanasia should be a consideration in the following scenarios

- Loss of production and/or failure to perform and/or failure to thrive (i.e., declining quality of life such as with advanced age, severe mastitis, chronic pneumonia etc.)
- Potential or known exposure to toxins (such as polyfluoroalkyl substances (PFAS) or lead toxicity) that would likely result in a food safety issue if sent to slaughter for human consumption
- Extended drug withdrawal time for clearance of tissue residue
- Behavior or temperament issues which render an otherwise fit animal to be unsafe
- Poor prognosis or prolonged expected recovery
- Diseases that could threaten herd health (i.e., BVD or others)
- Nonambulatory cattle that are not eating or which have not responded to treatment in 24 hours.

DECISION MAKING

Actions involving compromised cattle include treatment, slaughter or euthanasia. The following criteria should be considered when making a decision:

- If the animal is in severe pain, distress, or debilitation. Can appropriate relief be provided.
- Likelihood of recovery
- Ability to provide the compromised animal with sufficient feed and water
- Ability to provide an adequate environment and nursing through the full recovery
- Drug withdrawal if considering slaughter
- Economic considerations of treatment, slaughter or euthanasia
- Potential for pre- or post-mortem condemnation potential if sent to slaughter
- Diagnostic information that can provide additional insights to patient or herd
- Ability of animal to survive and have acceptable welfare during transport to slaughter facility
- Whether the animal poses a danger to people or other animals due to contagious disease or temperament.

Part of meeting our responsibility to reduce pain and suffering must be to see that euthanasia is provided promptly once the decision has been made. No more than four hours (preferably much less) should elapse between making the decision to euthanize and performing the procedure.

CONSIDERATIONS FOR SELECTION OF METHOD OF EUTHANASIA

When euthanasia is the most reasonable option

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for a compromised animal, the following elements should be considered to aid in the selection of the appropriate method:

- **Human Safety** The first consideration in the choice of euthanasia method is human safety. For example, the use of a firearm carries greater safety risks when compared to other methods.
- **Animal Welfare** All methods of euthanasia should produce a rapid death with no detectable pain and distress. Select a euthanasia technique that considers human safety as well as animal welfare and is appropriate for the specific situation.
- **Restraint** When performing euthanasia procedures, appropriate methods of restraint should be used. Some methods, such as captive bolt, require excellent restraint of the animal. Quality and availability of cattle chutes, halters, gates or other forms of restraint make certain forms of euthanasia more practical than others.
- **Practicality** An appropriate euthanasia technique must also be practical to use. For example, not all individuals responsible for carrying out euthanasia procedures have access to pharmaceuticals or firearms.
- **Skill** Certain techniques require skill and training to accomplish correctly. Individuals responsible for conducting euthanasia should be trained in proper euthanasia protocol and have access to appropriate, well-maintained equipment and/or medications.
- **Cost** Euthanasia options vary in cost. Specific techniques, such as firearms or captive bolts, require a greater initial investment, which may be defrayed over time.
- **Aesthetics** Certain euthanasia techniques, such as the use of a barbiturate overdose, may appear more humane to the general public when compared to other techniques. Some methods, such as a penetrating captive bolt, may cause significant involuntary movements by the animal that may be misinterpreted as a painful voluntary response to people inexperienced in bovine euthanasia. When selecting a euthanasia method, potential negative reactions by the animal or observer should be considered
- **Diagnostics** The selected euthanasia method should not compromise diagnostic sample collection (as in rabies testing). Some methods of euthanasia have not been studied for their impacts on diagnostic testing (i.e., intrathecal lidocaine [Aleman et al. 2015]). Veterinarians should use their best judgement when considering any possible post-mortem diagnostics that would be sought.
- **Carcass disposal** Carcass disposal is a critical consideration when selecting a euthanasia technique (Shearer et al. 2018). Carcasses must be handled and disposed of following state and federal regulations. Options may include rendering, burial, composting, incineration and potentially landfills. Cattle euthanized using a barbiturate overdose cannot be accepted at rendering facilities since the FDA has a tolerance and test for the drug in the rendered product. In some regions, regulations require animals euthanized with barbiturates to be incinerated or buried. Appropriate disposal of the carcass prevents scavenging and potential toxicity issues among wildlife. Any scavenging animals will be affected by carcasses with barbiturates, and this must be taken into consideration (Aleman et al. 2016). In addi-

tion, leachate from carcasses of barbiturate overdosed animals have the potential to contaminate other carcasses or the environment. Additionally, it is important to remember that even in death, animals in our care deserve respect, and dead animals should be handled with this in mind.

MECHANISMS OF EUTHANASIA

The agents of primary or adjunct euthanasia cause death by one of the three following mechanisms:

- Direct and swift depression of the central nervous system or organs necessary for life function (overdose with barbiturate or barbituric acid derivatives; intrathecal lidocaine hydrochloride administration). Hypoxia produced by inhaled agents is not recommended for ruminants.
- Hypoxia associated with agents or procedures that displace or block uptake of oxygen (such as that caused by exsanguination when used as an adjunctive method).
- Physical disruption of brain activity (such as that caused by gunshot, penetrating captive bolt, or pithing).
- Cardiac arrest triggered by intravenous administration of saturated potassium chloride (only acceptable as an adjunctive method following confirmation of unconsciousness)
- Neuromuscular blocking of breathing by intravenous administration of saturated magnesium sulfate (only acceptable as an adjunctive method following confirmation of unconsciousness)

Table 1: Recommended methods for practical euthanasia

Method	Risk to Human Safety	Skill Required	Potential Public Perception Issues	Adjunctive Method Required
Gunshot	high	moderate*	moderate: some blood and motion	no
Penetrating captive bolt	moderate	moderate*	moderate: some blood and motion	yes
Barbiturate or barbiturate derivative overdose	low	moderate*	perceived well	no
Two-step method (Anesthesia followed by intrathecal lidocaine or intravenous injection)	low	moderate*	perceived well	yes

*Operator Training Required

RECOMMENDED PRIMARY EUTHANASIA METHODS

1. Gunshot When properly executed, gunshot induces instantaneous unconsciousness and death, is inexpensive and does not require close contact with the animal. It should be emphasized that this method should only be attempted by individuals trained in the use of firearms and who understand the potential associated dangers (Longair 1991, Shearer 2008, Thomson et al. 2013, Griffin 2015, Shearer et al. 2018). Firearm options include rifles, handguns (pistols), or shotguns.

Rifles and Handguns Current recommendations suggest that the .22 caliber handgun or rifle loaded with a long rifle (LR) solid point bullet is sufficient for calves less than four months of age. In cattle over four months of age, it is necessary to use .22 Magnum or higher calibers for consistently

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Landmarks and placing the shot

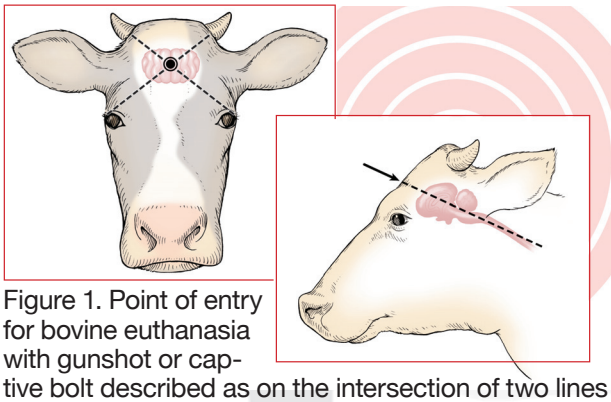


Figure 1. Point of entry for bovine euthanasia with gunshot or captive bolt described as on the intersection of two lines each drawn from the lateral canthus (outer corner) of the eye to the center of the base of the opposite horn (or where horn would be). *Courtesy Gilliam, Shearer, et al. 2012.*

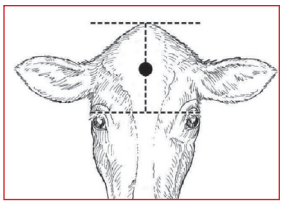
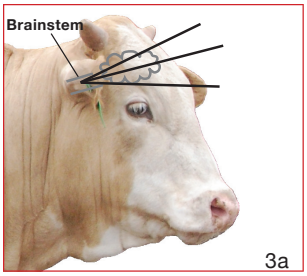
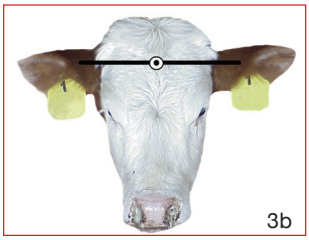


Figure 2. Alternate method: Selecting the proper anatomic site is to place the shot midway between a line connecting the lateral canthus of the eye and the poll on midline. *Gilliam, JN et al. 2016;*



3a



3b

Figures 3a and 3b. Alternate method of selecting the proper anatomic site is to aim the trajectory on midline between the base of the ears at the level of the external meatus and directed perpendicular or slightly downward (no more than 45 degrees). The angle may be modified as shown in Figure 3a to accommodate orientation of animal and caretaker, particularly when using a firearm. Penetrating captive bolts are typically discharged after holding the device flush and perpendicular with the frontal bone.
Courtesy R Dewell et. al. 2016.

effective euthanasia. The "AVMA Guidelines for the Euthanasia of Animals (2020)" recommends use of solid-point bullets. Muzzle energy available from a .22 Long Rifle is in the range of 100- to 150-foot pounds , whereas larger calibers such as the .38 Special, .357 Magnum or 9 mm will push muzzle energies well above the 300 foot pounds range. Rifles are capable of higher muzzle energies compared with handguns and are often a better choice in situations where a fractious animal must be shot from a distance.

Shotguns Shotguns are very lethal at close range (less than three feet from the point of intended entry), whether loaded with shotshells or slugs. The 12-, 16-, and 20-gauge shotguns are a good choice for euthanasia of adult cattle. The 28 or .410 gauge shotgun is an excellent choice for use in calf euthanasia. If using a shotgun loaded with shot shells, the operator should be very conscious of the distance from the gun barrel to the animal as projectiles will spread out into a larger pattern. Ideally, to obtain maximum consistency and efficacy of euthanasia, it is desired that the BBs from the shot shell make contact with the skull as a compact mass.

Placement of firearm When using a handgun, the firearm should be held within one to two feet of the intended target. The projectile(s) should be directed perpendicular to the front of the skull to minimize the likelihood of ricochet. In cattle, the point of entry of the projectile should be at the intersection of two imaginary lines, each drawn from the outside corner of the eye to the base of the opposite horn as shown in Figure 1. For operator and bystander safety, the muzzle of any firearm

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should never be held directly against the animal's head. Discharge of the firearm results in development of enormous pressure within the barrel that can result in explosion of the barrel if the muzzle end is obstructed or blocked.

Figure 4a. Penetrating captive bolt gun.

2. Penetrating captive bolt Captive bolt devices ("guns" or "stunners") are either penetrating or non-penetrating (Gregory & Shaw 2000, Grandin 2002, Humane Slaughter Association 2013, Kline et al. 2019, Casagrande et al. 2020). Only penetrating captive bolt devices are approved for euthanasia of mature bovines and, according to "AVMA Guidelines for Euthanasia of Animals (2020)", must not be used as the sole method of euthanasia. The bolt gun must be placed firmly against the skull at the same entry point previously described for a gunshot. Since use of the captive bolt gun requires close proximity to the animal, adequate restraint and prior sedation or tranquilization may be required. It is critical to maintain and clean the bolt gun as described by the manufacturer (Gilliam et al. 2012). Additionally, selection of cartridge strength may vary among manufacturers and the appropriate type and strength for the size of the animal must be used (Kamenik et al. 2019). Store cartridges in a cool dry area, away from humid environments. Exposing cartridges to moisture can affect burning of the propellant and thus lower the bolt speed and penetrating force. The optimal point of entry for the penetrating captive bolt is depicted in Figure 4b. When using a penetrating captive bolt, a secondary method of euthanasia must also be employed (as described below; Dersheid et al. 2016).

Figure 4b. Placement of captive bolt for optimal point of entry. Captive bolt should be held flush against skull and perpendicular with the frontal bone.

3. Barbiturate and barbituric acid derivatives When properly administered by the intravenous route, barbiturate overdose results in rapid loss of consciousness and death. When using sodium pentobarbital for this purpose, consult the label for the appropriate dose. When choosing a barbiturate for euthanasia, the barbiturate selected should be potent, long-acting, and stable in solution. The carcass of barbiturate treated animals is considered unfit for human or animal consumption. Ingestion of pentobarbital contaminated tissues by wildlife or rendered material consumed by domestic pets can induce toxicities, and all species are considered susceptible (FDA-CVM 2003 http://www.fda.gov/AnimalVeterinary/news Events/CVM updates/ucm119205.htm). Finally, as mentioned previously, the use of barbiturates limits carcass disposal options as renderers will not accept animals euthanized by this method. Due to scavenger risk, environmental contamination, and limited carcass disposal options, it is recommended that barbiturate overdose be a euthanasia tool of last resort.

COMMENT ON THE USE OF ALPHA-2 AGONISTS

It should be noted that the injection of xylazine or any other alpha-2 agonist has not been shown to induce anesthesia and is not acceptable to use for euthanasia either as the sole means or as the

primary method before applying an adjunctive method such as exsanguination, intrathecal lidocaine, potassium chloride, magnesium chloride or magnesium sulfate administration (Ef 2014, Dewell 2013). Animals must be rendered unconscious via general anesthesia, gunshot or captive bolt prior to administering one of the above secondary methods.

Alpha-2 agonists, such as xylazine, are sedatives that may provide safer handling of animals, and reduce the risk of further injury and distress, prior to euthanasia (Hanthorn & Sanderson 2019). However, the depth and duration of sedation in fractious, injured or otherwise compromised animals, especially after intramuscular or subcutaneous injection, can be unpredictable. Practitioners should ensure that the initial dose administered is adequate for deep sedation (for xylazine, 0.3 mg/kg bw IM or SC is recommended). Higher doses may be associated with convulsions and seizures that will make handling more dangerous and increase the risk of further injury. Animals sedated with alpha-2 agonists should be approached with caution and only when sufficient time has passed for the sedative to take full effect. Consideration should also be given to the potential environmental risk posed by alpha-2 agonist residues that may remain in the carcass at the time of disposal.

DETERMINATION OF UNCONCIOUSNESS

A state of apparent unconsciousness must be established immediately following the primary euthanasia procedure (Terlouw et al. 2015, Shearer 2018). In the field, the surrogate to unconsciousness is "lack of response" described below, as actual unconsciousness can only be determined by electroencephalography (EEG). The person performing the euthanasia must be prepared to immediately reapply an acceptable euthanasia technique if any sign of consciousness is demonstrated by the animal and detected by the observer. Secondary or adjunctive euthanasia methods must not be used until the animal has been determined to be unconscious.

Signs of unconsciousness

- Absence of corneal reflex
- Absence of vocalization
- Absence of gag reflex (no voluntary tongue movements or swallowing)
- Lack of rhythmic respiration
- No coordinated attempt to rise or right itself

SECONDARY OR ADJUNCT EUTHANASIA METHODS

Exsanguination, pithing and rapid intravenous injection of a solution of Potassium Chloride (KCl), Magnesium Sulfate ($MgSO_4$) or Magnesium Chloride ($MgCl_2$) are acceptable adjunctive methods. A second shot (penetrating captive bolt or gunshot) in the original frontal or poll location is an acceptable secondary choice of an adjunctive method when exsanguination, pithing or intravenous injection are not available.

1. Exanguination This method can be used to ensure death after stunning, anesthesia, or unconsciousness. It must not be used as a method for euthanasia of conscious animals. The most common exsanguination method in the bovine is to lacerate both the jugular veins and carotid arteries (Figure 5). A 6-inch-long sharp knife is fully inserted

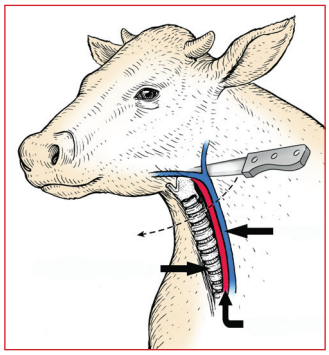

Figure 5. Exsanguination in a bovine *(Shearer 2008)*.

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behind the point of the jaw and directed downwards until blood is freely flowing. Alternatively, severing blood vessels of the brachial plexus may be performed by lifting a forelimb, inserting the knife deeply at the point of the elbow and cutting skin and vasculature until the limb can be laid back against the thorax of the animal. Another method is transecting the aorta via the rectum by a trained individual to pool blood within the abdominal cavity.

2. **Pithing** Pithing is an adjunctive technique designed to cause death by increasing the

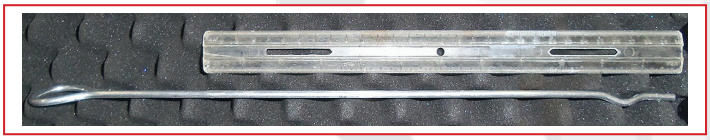

Figure 6. Pithing rod

destruction of brain and spinal cord tissue. It is performed by inserting a pithing rod or similar tool through the entry site produced in the skull by a bullet or penetrating captive bolt device. The operator manipulates the pithing tool to destroy both brain stem and spinal cord tissue, which results in death.

3. **Potassium Chloride (KCL)** Rapid IV administration of a solution of potassium chloride (KCl) induces cardiac arrest. Cattle must be anesthetized or unconscious prior to administration (Griffin 2015). The use of a captive bolt is also acceptable if a state of unconsciousness is achieved. The specific dose of KCl will vary according to the size of the animal, but an injection of 250 ml of a saturated KCl solution is usually sufficient for most mature cows. The KCl solution should always be given to effect (i.e., until death).

Potassium chloride can easily be sourced in the form of water softener salts and can be ordered in bulk off the internet. The typical concentration of KCl for use as a secondary method of euthanasia in ruminants is between 75-100 mg per kg of body weight. First, use a mortar and pestle (or another method) to grind the KCl crystals into a coarse powder. Next, dissolve the appropriate amount of KCl crystals in hot water (about 60 mls of water per 20 g of KCl). For reference, one tablespoon of KCl weighs approximately 20 grams. Maintain the KCl solution at room temperature to avoid precipitate formation. If precipitate forms, rewarm and remix the solution.

4. **Magnesium sulfate or magnesium chloride** Magnesium sulfate (aka $MgSO_4$, commonly referred to as "epsom salt") is a commonly available salt that has been classed as an antidysrhythmic and electrolyte (Medscape). When administered IV as a saturated solution, magnesium sulfate can affect both the central and peripheral nervous systems (Cooney and Titcombe, 2022). Administration of high levels of magnesium sulfate incites cardiac arrest by preventing calcium entry through voltage-dependent channels and reducing acetylcholine release at end-plates-thus inhibiting peripheral neuromuscular transmission and resulting in fatal cardiac arrest (Cooney and Titcombe; Messenger et al).

Similar to the use of saturated potassium chloride solution, magnesium sulfate can halt respiration prior to loss of consciousness, rendering it very inhumane. Thus, the administration of magnesium sulfate must not occur until a deep plane of anesthesia has been ascertained. Compared to rapid IV administration of a saturated potassium chloride solution, death may occur less rapidly when a saturated magnesium sulfate solution is administered (AVMA Guidelines for Euthanasia 2020).

To prepare a saturated $MgSO_4$ solution, a clean 5-liter container can be filled with 2 kg of

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$MgSO_4$. The container can then be "topped off" with clean, hot water. A layer of $MgSO_4$ at the bottom of the container is normal and evidence that the solution is saturated. The use of food dye to color the solution as well as careful labeling is recommended to prevent unintended usage. Used 500ml plastic bottles such as those used for calcium gluconate are often useful to store saturated $MgSO_4$ solution in. Prevent the solution from becoming too cold just prior to use; if the stored solution is exposed to colder temperatures, it may precipitate and clog the tubing and catheter/needle.

The volume required to cause death in an anesthetized animal ranges quite widely. Many practitioners figure approximately 500mls of a saturated $MgSO_4$ solution will kill most animals 450kg or less. It is advised to use a 14 gauge needle or catheter which can be secured with glue. A reusable IV tubing set such as Simplex© can be connected to the catheter/needle and the 500ml bottle of $MgSO_4$ solution and allowed to be administered via gravity flow. Sometimes, muscle fasciculations, stretching, agonal breaths, or clonic spasms are observed during or briefly after administration (Cooney and Titcombe; AVMA).

5. **Second shot** A properly aimed shot with an appropriate firearm or captive bolt, will reliably produce unconsciousness, but especially in the case of the captive bolt, may not lead to death (Casagrande et al. 2020). A second shot in an unconscious animal creates significant additional brain trauma, intracranial hemorrhage and substantial intracranial pressure. The increase in intracranial pressure often impairs regulation of respiratory and cardiac function within the medulla oblongata leading to death. If the first shot does not lead to immediate unconsciousness, a second shot in the original frontal or poll location (Robbins et al. 2021) is required immediately and is not optional.

6. **Intrathecal Lidocaine** A recently introduced method of euthanasia which has been studied in horses is intrathecal lidocaine administration following full anesthesia. Lidocaine is a common local anesthetic which works via sodium channel blocking in addition to other actions and is widely available in 2% sterile solution. Lidocaine has been widely used in both human and animal medicine as a spinal block causing direct anesthesia local nerves. The probable mechanism of death in the case of intrathecal lidocaine is related to the location and high dose of lidocaine resulting in direct anesthesia of vital cerebro-cortical and brainstem structures and secondary loss of respiratory and cardiovascular function (Aleman 2016).

With the patient under anesthesia the animal is positioned laterally and the head and neck is flexed to facilitate access to the atlantooccipital space. A spinal needle is used and advanced perpendicularly until cerebrospinal fluid can be aspirated. Following this the full dose of lidocaine is administered rapidly. In the research in horses and small ruminants the dose of lidocaine has been 4-5mg/kg using 2% lidocaine solution (Aleman 2016, Zolhavarieh 2011).

In a small study done on calf cadavers using dye the researcher demonstrated penetration to the anatomical structures responsible for consciousness (Rousseau 2019). In physiological studies the researchers observed an immediate loss of respirations followed by loss of electrical activity in the brain stem and finally slowing heart rate leading to cardiac arrest. Time to cardia arrest varied between species but took up to 15 minutes. (Aleman 2016,

Zolhavarieh 2011, Rosseau 2019). In one study looking at residues in horses they demonstrated residues from both the anesthetic agents (xylazine, midazolam and ketamine) and the lidocaine in low levels which would be below the dose expected to affect scavengers (Aleman 2016). However, proper carcass disposal is still recommended.

COMMENT ON POLL SHOOTING OR STUNNING

Poll position stunning with a penetrating captive bolt is not recommended as a primary method of euthanasia. However, recent peer reviewed literature has demonstrated there is no significant difference in the time to death (lack of respiration and heartbeat) when the poll shot is properly applied as a secondary shot in captive bolt euthanasia (Robbins et al. 2021). If using a gunshot or PCB behind the poll as a second shot, the shot should be directed toward the base of the tongue with proper positioning essential.

CONFIRMATION OF DEATH

Confirmation of death following a euthanasia procedure is absolutely essential regardless of what method of euthanasia is chosen. Keep personal safety in mind when confirming death because animals can make sudden involuntary movements. The primary indicator for confirmation of death is cardiac arrest. Lack of heartbeat and respiration for three-to-five minutes should be used to confirm death. The presence of a heartbeat can be best evaluated with a stethoscope placed under the left elbow. It should be noted that the heart continues to beat for a period of time with either captive bolt or firearm euthanasia, because heartbeat is controlled by the sino-atrial node and not the brain. Continued cessation of rhythmic breathing is considered a secondary indicator of death, and observation for movement of the chest can be used as an indicator of respiration in addition to lack of a heartbeat. However, respiration rates may be very erratic in unconscious animals; therefore, one must be cautious in the interpretation of respiration for confirmation of death. If respiration is not absent or the animal begins respiring again, a second shot is required. The corneal reflex may be tested by touching the surface of the eye. Normal or conscious animals will blink when the eye's surface is touched. Lack of a corneal reflex alone is not sufficient for confirmation of death, and by itself only proves the animal is unconscious. Continued monitoring of animals for a period of 20 to 30 minutes after euthanasia has been performed is also good advice to livestock owners and managers.

Figure 7. Confirmation of death

UNACCEPTABLE METHODS OF EUTHANASIA

Based on ethical and humane considerations, the following methods are considered unacceptable euthanasia techniques (AVMA 2020):

- Manually applied blunt trauma to the head of calves or mature cattle
- Injection of unapproved chemical agents or substances (e.g., disinfectants, non-anesthetic pharmaceutical agents)
- Sedation with an alpha-2 agonist such as xylazine followed by exsanguination, intrathecal lidocaine, potassium chloride, magnesium sulfate, or any other euthanasia method

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that requires the animal to be unconscious prior to its use
- Air injection into the vein
- Electrocution with a 120-volt electrical cord
- Drowning
- Exsanguination of conscious animals
- Inappropriate caliber of bullet for size of animal
- Puntilla—a method whereby a sharp pointed knife is plunged into the back of the animal's neck to sever the spinal cord by entry into the atlanto-occipital space

CONSIDERATION FOR EUTHANASIA OF CALVES AND BULLS

Calves and bulls require special consideration when selecting the proper method of euthanasia (Dewell et al. 2016). Ethical considerations do not change for the calf because it is small or more easily handled. As noted by USDA Food Safety Inspection Service, "A calf is a young bovine of either sex that has not reached puberty (up to about 9 months of age) and has a maximum live weight of 750 pounds." (USDA) Blunt trauma by physical blow to the head is not an acceptable method of euthanasia of calves because the skull is too hard to consistently achieve immediate and lethal destruction of brain tissue. This method is also difficult to consistently apply because of restraint and complications in positioning the calf for effective use of blunt force trauma methods. In addition to the methods outlined in Table 1 for mature bovines, using a purpose-built non-penetrating captive bolt stunner is an acceptable (with conditions) method of euthanasia for calves, but should be followed with an adjunctive step to assure death.


Figure 8. Consideration for bulls

The euthanasia of bulls presents unique challenges because of their size, temperament, and skull thickness. Operator safety is of primary concern in the euthanasia of bulls, and proper restraint at all times is critical. Bulls may be euthanized with specialized heavy-duty captive bolt guns or firearms capable of muzzle energies of 1000 foot-pounds, or by barbiturate overdose if proper carcass disposal options are met.

CONSIDERATIONS FOR EUTHANASIA OF BISON AND BUFFALO

The recommended method for the euthanasia of a bison is gunshot. A minimum of 1356 joules (J) (1000 ft-lb) of muzzle energy is required for the euthanasia of yearlings, cows and mature bulls. This limits the firearm options to higher caliber centerfire rifles (e.g. 30-30, 270, 30-06 and others). In one study, a 12-gauge shotgun with a 2.75-inch Foster slug was effective as a means of stunning bison heifers prior to on-farm slaughter for meat production (McCorkell et al. 2013). The majority of handguns produce muzzle energies well below 1356 J (1000 ft-lb) and would not be appropriate for euthanasia of mature bison (Galbraith et al. 2016).

The preferred anatomical site for entry of a bullet is on the forehead approximately 2.5 cm (1 inch) above an imaginary line connecting the bottom of the horns, which places the shot in a similar location to recommendations for mature cattle. Ideally, the angle of entry should be perpendicular to the skull. However, if it is necessary to shoot the animal from a distance, targets may be the

head (frontal or lateral side) or the thorax (heart shot; Galbraith et al. 2016). In cases where an animal is alert and holding the head elevated, a heart shot is preferable to avoid the bullet hitting the frontal bone at an angle that does not permit penetration (Rioja-Lang et al. 2019). This form of euthanasia should only be considered if proper restraint is not possible.

There are important anatomical differences that need to be considered when determining the best method of euthanasia for water buffalos compared with cattle. Skull bones are substantially thicker and the frontal and paranasal sinuses noticeably wider in buffaloes compared to cattle. Moreover, measures of the median distance from the frontal skin surface to the thalamus were 14.5 cm (11.7 cm–17.2 cm [4.6 inches to 6.8 inches]) vs 10.2 cm (10.1–12.1 cm [4 – 4.8 inches]) in water buffalos and cattle, respectively (Schwenk et al. 2016). The bolt length of conventional captive bolt devices is 9 to 12 cm (3.5 to 4.7 inches; Casagrande et al. 2020) meaning that the ability of the bolt to make direct contact with the thalamus and brainstem is less likely using frontal sites in water buffalos compared with cattle. For this reason, the use of the PCB at frontal sites in water buffalos is generally less effective (Gregory et al. 2009).

Anatomic Site for conducting euthanasia of bison The preferred anatomic site for entry of a bullet is on the forehead approximately one inch above an imaginary line connecting the bottom of the horns (Galbraith et al. 2016). Alternatively, the site can be identified on the intersection of lines from the lateral canthus to the top of the horn, which is similar to landmarks used in cattle. While it may be difficult to achieve the perfect angle the goal is for the bullet to enter perpendicular to the skull and travel through the brain and brain stem by aiming for the foramen magnum.

Anatomic sites for conducting euthanasia of water buffalo Recommendations for euthanasia of water buffalo with a firearm using frontal sites are to direct the projectile on the intersection of two imaginary lines connecting the lower edge to the upper edge of the contralateral horn (Schwenk et al. 2016). This site is above a line drawn laterally connecting the bottom of the horns. Depending upon the size of the horns this will be at a higher or lower location.

CONSIDERATIONS FOR LIVE FETOTOMIES

A fetotomy is defined as dismemberment of a fetus in utero to aid its delivery via the birth canal. The purpose of a fetotomy is to save the life of the dam. It is typically reserved for cases in which the fetus is dead (or presumed dead) and intractable dystocia. In rare cases, the only way to save a dam is to perform a fetotomy on a live calf, which comes with understandable ethical concerns over whether calves can feel pain and distress. Ruminant fetuses are sentient and have the neural apparatus necessary to feel both positive and negative states, but are under a hormonally induced unconsciousness, which prevents any sensation or noxious stimulus to be perceived (Mellor & Diesch 2006). Evidence from Mellor (2010, 2012) demonstrates that farm animal fetuses remain in an unconscious state throughout late pregnancy and birth and that newborns only become conscious when they have successfully inhaled air into their lungs. In fact, fetal unconsciousness may become deeper during states of transient hypoxemia (as in natural labor or prolonged dystocia). According to Mellor, a calf that has not breathed atmospheric oxygen is not conscious and thus cannot perceive pain. That said, fetotomies on live calves should be restricted to cases where no other dystocia management option exists to preserve the life of the dam.

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There are many techniques that can be attempted to determine if a fetus is alive in utero. These include: feel for pulse in the umbilical cord; strongly pinching the tongue, lip, or anus; by applying strong pressure to the supraorbital ridge of the eye socket; or eliciting a leg withdrawal in response to being pulled or pedal reflex stimulation. The movement or withdrawal responses are reflexes to pressure and are not signs indicating fetal conscious awareness. Fetuses that move in response to a noxious stimulus in utero remain hypoxemic and are still considered to be unconscious as judged by EEG evidence (Mellor et al. 2005, Mellor 2010).

Although current studies demonstrate fetal unconsciousness prior to oxygen inhalation, veterinarians may consider euthanasia of the calf prior to dismemberment if feasible. If the umbilical cord can be reached it can be severed manually and fetotomy can continue two to three minutes after cord severance (Mellor 2013). If the head is accessible, the fetus can be euthanized by cutting the throat and exsanguinating before starting the fetotomy. Decapitation using a fetotomy wire will offer the same result if performed expediently.

TRAINING REQUIREMENTS

If euthanasia is to be provided by the owner, employees of the facility, or a non-veterinarian third party, the expectation is that those individuals should have annual training and certification (Turner & Doonan 2010). Each individual must know how to recognize animals in need of euthanasia, proper euthanasia technique, how to properly confirm death, safe use of the methods of euthanizing to be employed, as well as how to maintain the equipment after and between uses. Some documented record of this training should be kept in the facilities training records or herd health plan.

RECORDS AND RECORD KEEPING

Keeping accurate and complete records is an important part of providing euthanasia. Records should include, at a minimum, the ID of all animals euthanized, the date, the person providing euthanasia, the indication of the reason for euthanasia, method of euthanasia and the carcass disposal utilized. Records should be maintained in accordance with the state's requirements for medical records. Records should also be kept for the euthanasia equipment. This should include a gun or captive bolt cleaning and service logs. Properly functioning equipment is critical to rendering the animals immediately insensible.

CONCLUSION

Personnel at sites that routinely handle cattle should be prepared with the knowledge, necessary skills, and well-maintained equipment to conduct euthanasia. Penetrating captive bolt and gunshot are the only two acceptable methods typically available to non-veterinarians for emergency euthanasia of cattle. Animal transporters should also be properly trained in euthanasia techniques and have contact information for appropriate personnel in case of an emergency. An action plan for routine and emergency euthanasia should be developed and followed wherever animals are handled. Dead animals should be disposed of promptly and according to all federal, state, and local regulations. Persons who perform humane euthanasia must be technically proficient, mentally capable, and possess a basic understanding of the anatomical landmarks and equipment used. If there is any degree of question or discomfort with a proposed euth-

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anasia procedure, a veterinarian should be consulted.

Additionally, it is important to remember that even in death, animals in our care deserve respect, and dead animals should not ever be handled in a manner that would be unacceptable for a live non-ambulatory cow. Acceptable methods for moving the carcass would include placing them onto a sled or rolling them into a bucket. If cattle are to be dumped into a container or pit, care should be taken to use the minimum height possible in order to minimize the distance the carcass will fall.

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AABP JUDICIOUS THERAPEUTIC USE OF ANTIMICROBIALS IN CATTLE

The AABP is committed to antimicrobial stewardship, which includes an emphasis on preventive health programs including husbandry, biosecurity, routine examinations and immunization. These guidelines are intended as an aid in preserving the effectiveness and availability of antimicrobial drugs through conscientious oversight and responsible medical decision making, while safe-guarding animal, public and environmental health.

The AABP recognizes that antimicrobials remain necessary for animal health to treat, prevent and control infectious disease in beef and dairy cattle and emphasizes that preventive health programs can reduce the occurrence of disease and therefore the need for antimicrobials.

Antimicrobial stewardship refers to the actions veterinarians take individually and as a profession to preserve the availability and effectiveness of antimicrobial drugs through conscientious oversight and responsible medical decision making while safe-guarding animal, public and environmental health. Such stewardship involves maintaining animal health and welfare by implementing a variety of preventive and management strategies to prevent common diseases; using an evidence-based approach in making decisions to use antimicrobial drugs; and then using antimicrobials judiciously, sparingly and with continual evaluation of the outcomes of therapy, respecting the client's available resources. Following are the AABP's general guidelines for the judicious use of antimicrobials in beef and dairy cattle.

- The veterinarian's primary responsibility is to help design management, immunization, housing and nutrition programs that will aid in reducing the incidence of disease and the need for antimicrobials.
- Antimicrobials should only be used if there is a valid reason, after consideration of therapeutic alternatives, and within the confines of a valid veterinarian-client-patient relationship. These guidelines apply to both dispensing of antimicrobials and issuance of prescriptions or veterinary feed directives.
- Veterinarians should properly select, prescribe and use antimicrobial drugs:
  - The veterinarian should select an antimicrobial drug, product and regimen that is likely to be effective given strong clinical evidence of the identity of the pathogen causing disease and based on clinical signs, history, necropsy examination, laboratory data and clinical experience.
  - Treatment programs should reflect best-use principles. Regimens for antimicrobial use should be optimized using current pharmacological and microbiological information and principles. This includes using antimicrobials at an appropriate dosage, for the shortest appropriate period, and in the smallest number of animals reasonable. The use of antimicrobials should be based on an evaluation of animal-specific risk factors rather than standard practice.
  - Whenever possible, label instructions should be followed to include using antimicrobials labeled for the condition diagnosed following the labeled, dose, route, frequency, duration and withholding period.
  - Extralabel drug use must occur only within the provisions of the AMDUCA regulations.
  - Compounding of antimicrobials from bulk compounds for use in cattle is prohibited.
  - Combination antimicrobial therapy should be discouraged unless there is information to show an increase in efficacy or suppression of resistance development.

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AABP JUDICIOUS THERAPEUTIC USE OF ANTIMICROBIALS IN CATTLE

- Drug integrity should be protected through proper handling, storage and observation of the drug's expiration date.

■ Veterinarians prescribing antimicrobials should aspire to ensure proper use in the production facility through oversight of all antimicrobials used, regardless of where they were purchased.

- Prescription or dispensed drug quantities should be appropriate to the production unit size and expected need, so that stockpiling of antimicrobials on the production unit is avoided.
- The veterinarian should have a role in training production facility personnel who use antimicrobials. This training should include indications, dosages, withdrawal times, route of administration, injection site precautions, storage, handling, record keeping and accurate diagnosis of common diseases. The veterinarian's role should be ongoing to ensure that all employees remain current on antimicrobial use.
- Veterinarians are encouraged to provide written or computerized treatment protocols to clients that describe indications, meat and milk withdrawal times, and instructions for antimicrobial use in the production facility. All FDA record-keeping requirements must be followed.
- The veterinarian should regularly monitor antimicrobial use on the production facility by reviewing and reconciling treatment records, drug inventory and drug purchase history. The veterinarian should monitor labels to ensure that they are accurate and that the labels will enable animal caretakers to correctly use antimicrobials.
- Veterinarians should participate in continuing education programs that address therapeutics and antimicrobial resistance.

Approved by the AABP Board of Directors, October 2013
Revised by the Committee on Pharmaceutical and Biologics Issues and approved by the AABP Board of Directors, March 2019

JOINT AABP-AVC JUDICIOUS THERAPEUTIC USE OF MEDICALLY IMPORTANT ANTIMICROBIALS IN CATTLE

The AABP and the AVC are committed to antimicrobial stewardship, which includes an emphasis on preventive health programs including husbandry, biosecurity, routine examinations, and immunization.

These guidelines are intended as an aid in preserving the effectiveness and availability of medically important antimicrobial drugs through conscientious oversight and responsible medical decision-making, while safe-guarding animal, public and environmental health.

The AABP and the AVC recognize that medically important antimicrobials remain necessary for animal health to treat, prevent, and control infectious disease in beef and dairy cattle and emphasize that preventive health programs can reduce the occurrence of disease and therefore the need for antimicrobial therapy.

Antimicrobial stewardship refers to the action that veterinarians take individually and as a profession to preserve the availability and effectiveness of antimicrobial drugs through conscientious oversight and responsible medical decision-making while safe-guarding animal, public and environmental health. Such stewardship involves maintaining animal health and welfare by implementing a variety of management strategies to prevent or reduce common infectious diseases; using an evidence-based approach in making decisions to use antimicrobial drugs; and then using antimicrobials judiciously, sparingly, and with continual evaluation of the outcomes of therapy, respecting the client's available resources. Following are the AABP and AVC's general guidelines for the prudent use of antimicrobials in beef and dairy cattle.

1 The veterinarian's primary responsibility is to help design biosecurity and biocontainment programs which include appropriate immunization, housing and nutritional components that will aid in reducing the transmission and incidence of infectious diseases and the need for antimicrobials.

2 Antimicrobials should only be used if there is a valid reason, after consideration of therapeutic alternatives, and within the confines of a valid veterinarian-client-patient relationship. These guidelines apply to both dispensing of antimicrobials and issuance of prescriptions or veterinary feed directives.

3 Veterinarians should properly select, prescribe, order, and use antimicrobial drugs considering the therapeutic intent of prevention, control, or treatment:

a. The veterinarian should select an antimicrobial drug, product and regimen that is likely to be effective given the therapeutic intent, strong clinical evidence of the identity of the pathogen causing disease and based on clinical signs, history, necropsy examination, laboratory data, clinical experience, or epidemiological evidence. Therapeutic use does not include the use of antimicrobial drugs for purposes of production enhancement.

b. Therapeutic plans should reflect best use principles. Regimens for antimicrobial use should be optimized using current pharmacological and microbiological information and principles. This includes using antimicrobials at an appropriate dosage and route of administration, for the shortest appropriate period, and in the smallest number of animals reasonable. The use of antimicrobials should be based on an evaluation of animal-specific risk factors rather than standard practice.

c. Whenever possible, label instructions should be followed to include using antimicrobials labeled for the condition diagnosed following the labeled, dose, route, frequency, duration, and withholding period.

d. Extra-label drug use must follow all relevant laws and regulations.

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e. Compounding of antimicrobials from bulk drug substances for use in cattle is prohibited.

f. Combination antimicrobial therapy should be discouraged unless there is information to show an increase in efficacy or suppression of resistance development.

g. Drug integrity should be protected through proper handling, storage and observation of the expiration date.

4 Veterinarians prescribing antimicrobials should aspire to ensure proper use in the production facility through oversight of all medically important antimicrobials.

a. Prescription or dispensed drug quantities should be appropriate to the production unit size and expected need so that stockpiling of antimicrobials on the production unit is avoided.

b. The veterinarian should have a role in training production facility personnel who use antimicrobials. This training should include indications, dosages, withdrawal times, route of administration, injection site precautions, storage, handling, record keeping and accurate diagnosis of common diseases. The veterinarian's role should be an ongoing one to ensure that all employees remain current on antimicrobial use.

c. Veterinarians are encouraged to provide written or computerized treatment protocols to clients that describe indications, meat and milk withdrawal times, and instructions for antimicrobial use in the production facility. All FDA record-keeping requirements must be followed.

d. The veterinarian should regularly monitor antimicrobial use on the production facility by reviewing and reconciling treatment records, drug inventory, and drug purchase history. The veterinarian should monitor labels to ensure that they are accurate and that the labels will enable animal caretakers to correctly use antimicrobials.

e. Veterinarians should participate in continuing education programs that address therapeutics and antimicrobial resistance.

f. Veterinarians are encouraged to evaluate the safety and efficacy of all antimicrobial modalities as information becomes available.

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.

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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

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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,

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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.[1, 2] 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).

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.[3] 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

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variations preclude comparisons among vaccines. Cautionary statements on the USDA website direct the end-user to consult with a licensed veterinarian for the interpretation of the publicly available data. https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/product-summaries/product-summaries

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 animals[6, 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-

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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.[4] 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.[5] 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.

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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."* [8]

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.[9] The pertinent definitions were captured in 9 CFR 101.2.[10]

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."[11]

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.

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- Contact information of those reporting the event.
- The details of the event.
  - **Contacting the Manufacturer** The CVB encourages the public to submit adverse event reports to the manufacturer of immunobiological products. Many manufacturers maintain veterinary technical services departments to handle such reports and may also offer diagnostic advice, treatment recommendations and guidance on product use. *Please note that reporting adverse events to the manufacturer cannot be done from the website. The reporter will need to contact the manufacturer directly.* A contact telephone number may be available on the label of the product.
  - **Center for Veterinary Biologics** Once an adverse event has been reported to the manufacturer, the CVB may be contacted.
    - **Online** (preferred method): USDA Adverse Event Reporting
    - **Fax or mail** Download and complete the Adverse Event Report Form (APHIS 2080) and FAX to (515) 337-6120 or submit to the CVB by mail at:
      Center for Veterinary Biologics
      1920 Dayton Avenue
      P.O. Box 844
      Ames, Iowa 50010
    - **Telephone** Call the CVB at 800.752.6255.

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.[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
  - Examples
    - 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.

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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

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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.

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- 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.

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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 refrigerator temperature, 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.[18]

- 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

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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:[12]
  - 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.

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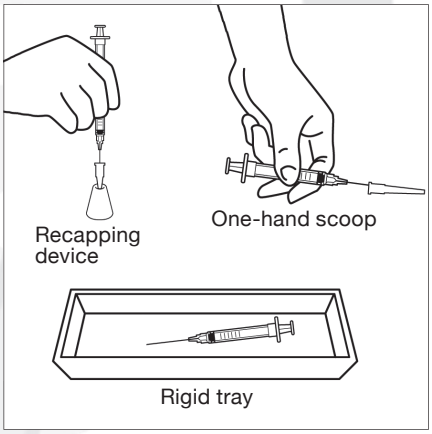
- Needles are designed to be single-use products and contain a coating that assists in gliding during administration. Multi-use of a single-use needle will dull the needle, lose the assisting coating, and result with increased risk of tissue damage.
- Follow the correct withdrawal times for slaughter 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.



- Alternatively, 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,

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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.

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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
  - Attenuated
    - 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.
      - The vaccine should be boosted on an annual basis ~40 days prior to breeding.
      - For a more complete discussion on the use of MLV IBR vaccines in pregnant animals see the section on adverse events.
  - 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.
    - Immune response may be negatively impacted by presence of maternal antibody—a variable impact.
    - Available in combination with killed BVD vaccine.
- Modified Live Intranasal
  - Attenuated
    - 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

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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.[25] 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

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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.
    - No monovalent vaccines currently available.
  - 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.
    - No monovalent vaccines currently available.
  - Modified Live Parenteral
    - Attenuated
    - Immune response may be negatively impacted by presence of maternal antibody.

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- 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. septicum, 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.

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- **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.[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

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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

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respiratory antigens. Vaccination for Hardjo-bovis can prevent colonization and significant urinary shedding by vaccinates.[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.[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.[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.[37] Two doses of the vaccine are recommended to achieve a protective antibody level.[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.[37]

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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

- This is a modified-live rough mutant strain of *Brucella* and should be handled carefully by veterinarians during the mixing and vaccination process. Human exposures to this vaccine (accidental injection, ocular exposure, etc.) should be reported immediately to a physician for treatment recommendations.
- 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

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and stress.[42, 43] 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.[41] 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.[44] 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.[45] Additionally, most multivalent clostridial vaccines do not contain *C. tetani* antigens.[46] Vaccination for

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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.

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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.[51, 52, 54, 55] 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.[53] A single conditionally licensed vaccine for *M. bovoculi* is available, however its efficacy is also not supported in the current literature.[50] 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.[56, 57] 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-

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trolled field trials in dairy calves.[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.[58] In some instances, vaccinates in clinical trials have experienced more severe disease than non-vaccinated controls.[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.

■ Vaccination Schedule Notes

- The available licensed vaccines for *Mycoplasma bovis* are killed bacterins.
- Both single dose administration and a boostered vaccine series are recommended with the approved vaccines, depending on the label.

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. chauvoe*i. 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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ESTABLISHING AND MAINTAINING THE VETERINARIAN-CLIENT-PATIENT RELATIONSHIP IN BOVINE PRACTICE

The veterinarian-client-patient relationship (VCPR) is an integral part of veterinary oversight of animal health and proper drug use on cattle operations. State and federal codified VCPRs regulate the practice of veterinary medicine legislatively. This document describes non-regulatory management practices endorsed by the American Association of Bovine Practitioners (AABP) as general guidelines for its members to refer to during their course of practice.

THE AABP IDENTIFIES THE FOLLOWING AREAS THAT ARE CRITICAL COMPONENTS FOR ESTABLISHING AND MAINTAINING A VCPR:

■ WRITTEN AGREEMENT

Maintain written agreements for working relationships

A veterinary practice or individual should establish a written agreement with the client that identifies the veterinarian (or veterinary practice if multiple veterinarians from one clinic provide service) who is accountable for drug use and treatments administered to cattle on the operation. If more than one veterinarian or veterinary practice has a working relationship on the operation, then the agreement should establish which one has the overall responsibility for treatment protocols, prescriptions, personnel training, oversight and drug use on the operation. The identified veterinarian is referred to as the Veterinarian of Record.

■ VETERINARY OVERSIGHT

Have a Veterinarian of Record

The Veterinarian of Record is responsible for making recommendations with respect to the animal health at the operation, including appropriate oversight of drug use on the operation. Such oversight is a critical component of establishing and validating a VCPR. This oversight should include, but may not be limited to, establishment of treatment protocols, training of personnel, review of treatment records, monitoring drug usage and assuring appropriate labeling of drugs. Veterinary oversight of drug use should include all drugs used on the operation regardless of the distribution of drugs to the operation. Regular site visits are an essential component to providing such oversight, however this can be supplemented through laboratory data evaluation, records evaluation, telephonic and electronic communication. The timeliness of site visits should be determined by the Veterinarian of Record based on the type and size of the operation.

■ RELATIONSHIP WITH CONSULTANTS AND OTHER VETERINARIANS

Clarify any and all relationships with consultants and other veterinarians

If a veterinarian who is not the Veterinarian of Record provides professional services in any type of consultative or advisory capacity, then it is incumbent on that veterinarian to ensure that the Veterinarian of Record is contacted and informed of their findings and recommendations. No protocols or procedures that have been established by the Veterinarian of Record should be changed unless or until there is an agreement by all parties about such changes. The agreement between the Veterinarian of Record and the client should establish which management groups of the operation are covered in the agreement. For instance, reproduction, milk quality, youngstock/replacement, feedlot, cow-calf and sick animal treatments are possible identifiable areas.

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ESTABLISHING AND MAINTAINING THE VETERINARIAN-CLIENT-PATIENT RELATIONSHIP

■ TREATMENT PROTOCOLS

Provide written protocols

Protocols and treatment guidelines for commonly occurring, easily recognizable conditions should be established in writing and agreed upon by all parties involved, signed and dated. Training of personnel authorized to use drugs on the operation should be undertaken and periodically reviewed. The frequency of such training and review should be determined by the size and type of the operation, the rate of personnel turnover, and the changes in protocols and procedures. The treatment protocols and procedures should include all drugs used on the operation (Over-The-Counter, prescription, extra-label, Veterinary Feed Directive, water-soluble). All protocols should clearly define when to quit treating and seek professional help (poor response, increase in severity of clinical signs).

■ WRITTEN/ELECTRONIC TREATMENT RECORDS

Ensure written or electronic treatment records are maintained

Written/electronic treatment records of all animals or groups of animals treated are an essential component of maintaining and establishing the VCPR to decrease the risk of violative drug resides. Such records should include, at a minimum, the date, identification of animal(s), drug(s) used, frequency, duration, dose, route, appropriate milk/meat withdrawal intervals and the person administering the treatment. Periodic and timely review of the treatment records and drug usage is an important part of oversight by the Veterinarian of Record.

■ PRESCRIPTION DRUGS

Provide drugs or prescriptions for specific time frames and for specific protocols

Provision of drugs or drug prescriptions should be for specific time frames and appropriate to the scope and type of operation involved and only for management groups within the operation that the Veterinarian of Record has direct involvement and oversight. Additionally, failure to follow agreed upon protocols and procedures should be grounds for denial of provision of drugs or prescriptions except for an individual patient needing treatment at the time of examination. Routine examination of drug inventories on farm and product purchase records (pricing information is unnecessary) review are recommended. Cooperation with distributors is encouraged. Establishment of a VCPR for the sole purpose of the sale of drugs or increased sales of a particular brand of drug is not a valid or ethical reason for having a VCPR.

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