BRD is complicated.

Fortunately, your choice for vaccination against BRD is simple: **Merck Animal Health Intranasal Vaccines.**

MERCK
Animal Health

Bovine Respiratory Disease (BRD) develops as a result of complex interactions between pathogens, environmental factors and the animal's immune system.

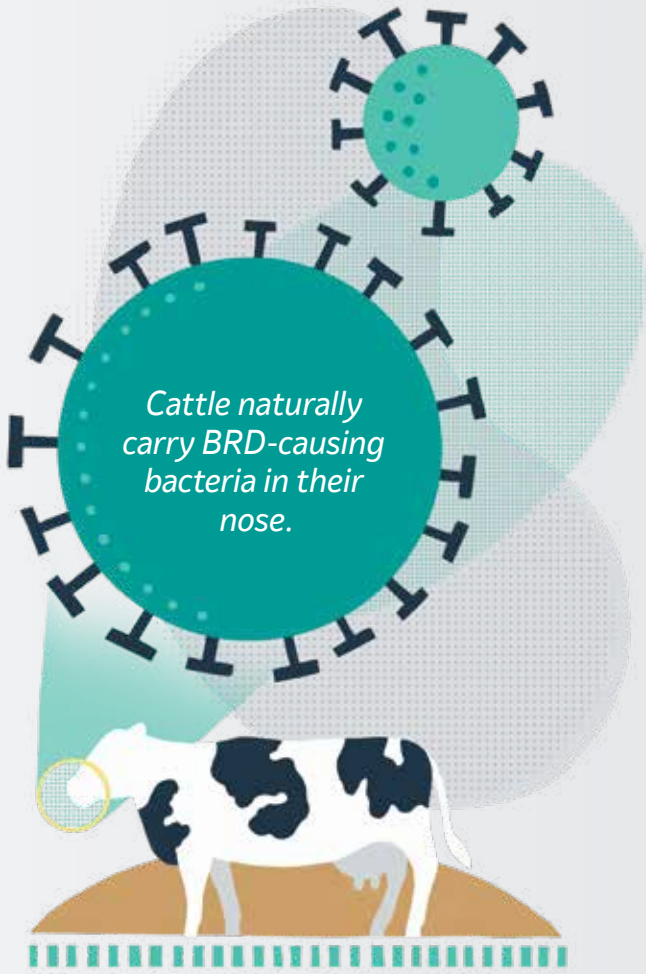
BRD: The Big Five

1. Infectious Bovine Rhinotracheitis virus (IBR)
2. Parainfluenza virus (PI_3)
3. Bovine Respiratory Syncytial virus (BRSV)
4. *Mannheimia haemolytica* bacteria
5. *Pasteurella multocida* bacteria

THE PATHOGENS

Viruses can cause pneumonia directly (for example, BRSV) or damage natural resistance mechanisms leading indirectly to bacterial pneumonia (for example, IBR damages mucus-clearing cells lining the trachea, leading to decreased ability to clear bacteria from the lungs).

Bacteria can also cause BRD. *M. haemolytica* and *P. multocida* are the most frequently isolated bacteria from pneumonic lungs in cattle. Interestingly, they are both part of the normal bacterial flora of the nose and throat of cattle. As long as the animal's immune system is not compromised by stressors and its respiratory tract isn't damaged by viruses or irritants, these bacteria pose little threat. When the respiratory tract is compromised, pneumonia can develop very rapidly.



THE ENVIRONMENTAL FACTORS

Stressors decrease the immune system's ability to respond to challenges. Examples of stressors include weaning, transportation, dehydration, commingling, castration, dehorning, crowding and bad weather.

Irritants damage the upper respiratory tract. Examples of irritants are dust, ammonia and exhaust fumes.

When cattle are in crowded environments, particularly under a roof, transmission of pathogens between animals increases.

THE ANIMAL'S IMMUNE SYSTEM

Cattle have a robust immune system and, in the absence of an overwhelming pathogen challenge or adverse environmental factors, are very resistant to disease. However, there are factors that can decrease or increase an animal's ability to respond to disease challenge.

Factors that decrease resistance to disease challenge – i.e., compromise the immune response:

- Dehydration
- Inadequate energy or protein
- Mineral deficiency – particularly selenium
- Intestinal parasitism
- In young calves: Failure to receive adequate passive transfer of antibodies via colostrum

Increased resistance to disease challenge can be achieved through vaccination:

- Vaccines are used to prime the immune system to be ready to act quickly to help to eliminate pathogens before they can cause disease

VACCINATION – The Basics

When an animal “sees” a pathogen for the first time, it must first recognize the pathogen as foreign and then respond to it.

This takes time and the pathogen can cause disease in the interim. Following this, the animal develops immune “memory” for that pathogen and can respond much more quickly to a subsequent exposure.

Vaccines show the animal what the pathogen in the vaccine “looks like.”

When the animal’s immune system “sees” the pathogen again, it can respond much more quickly and help to eliminate the pathogen prior to the development of disease.

VACCINATION – The Advanced Course

What the viral or bacterial foreign invader (pathogen) “looks like” is called its antigenic appearance, created by a unique combination of surface antigens.

Dendritic cells are the ever-vigilant guards of the body. When they detect a foreign pathogen, they latch onto it and carry it to a lymph node or other lymphoid tissue.

There, T-lymphocytes (T-cells) and B-lymphocytes (B-cells) begin the immune response – both to eliminate the pathogen and develop immune memory.

T-cells are particularly important in protecting against viral infections.

B-cells produce antibodies (immunoglobulins) – including IgG (the most common antibody) and IgA (the antibody found on mucosal surfaces, including those of the respiratory tract).

ADVANTAGES OF INTRANASAL VACCINATION

Most respiratory infections start from a mucosal surface – primarily the nose. With intranasal administration, initiation of the immune response can occur quickly, reliably and effectively.

- There is abundant lymphoid tissue in the nose and throat – where dendritic cells can present antigen to T- and B-lymphocytes
- Intranasal administration typically leads to production of IgA, which is the protective antibody needed at mucosal surfaces[1]
- Some intranasal vaccines also lead to production of IgG, which is the protective antibody needed within the body, including within lung tissue[2-4]

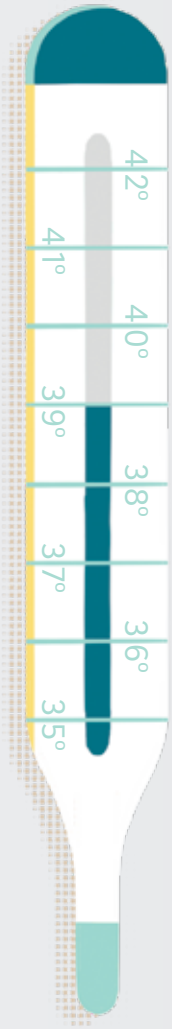
Intranasal vaccination is effective in the face of maternal antibodies.

- Historically, it was believed that in calves less than 3 to 4 months of age, antibodies (IgG) from colostrum would bind to and inactivate a parenterally (SQ or IM) administered vaccine before it could stimulate an immune response. While there are exceptions to this, it is still largely true.
- Intranasal vaccination is effective in the face of maternal antibody. With intranasal delivery, there is little to no opportunity for maternally derived IgG to interfere with the immune response.[5]

Intranasal vaccination is needle free – an obvious advantage with respect to Beef Quality Assurance.

ADVANTAGES OF MODIFIED LIVE VACCINES

Lower antigenic load = less stress on the animal



- In order to elicit an immune response, killed vaccines generally contain large numbers of organisms/large amounts of antigen (also known as antigenic load) plus potentially irritating chemical adjuvants, which are necessary to stimulate an immune response. Modified live vaccines contain organisms that have been changed so that they cannot cause disease but can still replicate within the animal. Modified live vaccines effectively stimulate immunity while containing fewer organisms (less antigenic load).
- For intranasally administered vaccines, more replication on the mucosal surface is generally better. More replication leads to greater stimulation of the immune system which leads to better immunity. Some vaccines contain "temperature-sensitive" IBR that does not replicate at temperatures above 39°C (102.2°F). While the temperature in the nasal cavity of cattle is typically lower than this, it can reach 39°C in high ambient temperature conditions, potentially hindering replication of a temperature-sensitive vaccine.[6] The IBR in BOVILIS® NASALGEN® vaccines has a 50-year history of both safety and efficacy, and has been shown to be efficacious in high ambient temperature conditions.[4]

Interferon response from intranasally administered modified live IBR

- Interferon (IFN) is a signaling protein released in response to the presence of viruses, causing nearby cells to heighten their antiviral defenses. IFN can also directly inhibit viral replication. Indeed, interferon was named for its ability to "interfere" with viral replication.
- The IBR antigen in BOVILIS® NASALGEN® IP elicits a rapid interferon response, which provides nonspecific protection against many viruses. Through this, cattle are protected early on as they develop a serum (IgG) and mucosal (IgA) antibody response.[7]

In a recent study[7] comparing vaccination with either BOVILIS® NASALGEN® IP or Inforce 3®:

- BOVILIS NASALGEN IP vaccinated calves had significantly higher levels of IFN-α on Day 5 after vaccination.
- BOVILIS NASALGEN IP vaccination stimulated production of IFN-α in a significantly higher proportion of calves on Day 5 after vaccination. Of the BOVILIS NASALGEN IP vaccinaced calves, 66% had detectable IFN-α compared to 33% of Inforce 3 calves.
- Similar to IFN-α, on Day 5 after vaccination, BOVILIS NASALGEN IP stimulated numerically higher levels of IFN-γ in a numerically greater proportion of calves. Of the BOVILIS NASALGEN IP vaccinated calves, 87% had detectable IFN-γ compared to 63% of Inforce 3 calves.
- BOVILIS NASALGEN IP stimulated a numerically greater nasal IgA vs. BoHV-1 antibody response on Days 21 and 42 after vaccination compared to Inforce 3.
- In general, calves vaccinated with BOVILIS NASALGEN IP had a more robust immune response.

Does concurrent administration of an antibiotic adversely affect the efficacy of intranasally administered bacterial BRD vaccines?

- To answer this question, a recent study[8] evaluated the effect of tildipirosin on the efficacy of a concurrently administered vaccine containing the same *Mannheimia haemolytica* fraction as ONCE PMH® IN and BOVILIS® NASALGEN® 3-PMH in 14-week-old Holstein or Holstein-cross calves. Experimental groups were 1) IN vaccine only; 2) IN vaccine + tildipirosin subcutaneously; 3) IN placebo; and 4) IN placebo + tildipirosin subcutaneously.
- Seventy days after enrollment, the calves were challenged with virulent *M. haemolytica*. Seven days after challenge, the calves were euthanized, and a percent lung lesion score (LLS) was assigned to each. There was no significant effect of tildipirosin on LLS for IN vaccinated calves or those receiving the IN placebo vaccine. However, IN vaccination with or without tildipirosin resulted in significantly lower LLS. Therefore, under the conditions of this study, concurrent administration of tildipirosin did not interfere with the efficacy of the vaccine.

Talk to a technical service veterinarian for additional trial data as well as the importance of immunity to *M. haemolytica* leukotoxin.

Three Critical Factors for Successful Vaccination

1. **An effective vaccine:**

   Merck Animal Health intranasal vaccines have been shown to be both safe and effective.

2. **Appropriate stimulation of the immune system:**

   Merck Animal Health intranasal vaccines can be given in the face of maternal antibody. Maternal antibody may decrease the efficacy of parenterally administered vaccines in calves less than 3-5 months of age.

3. **Administration of the vaccine prior to exposure:**

   When a vaccine cannot be given prior to a stress-causing event, BOVILIS NASALGEN IP elicits an interferon response that can help bridge the gap until antibody production begins.[9]

Simplify BRD prevention with vaccination that's right on the nose.

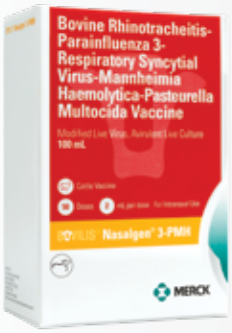
With intranasal vaccines from Merck Animal Health, initiation of the immune response can occur quickly, reliably and effectively.

MERCK
Animal Health

Cattle Intranasal Vaccine Portfolio

Protection has never looked better.

The same trusted Merck Animal Health vaccines you've relied on for years, now with new packaging.



NEW BOVILIS® NASALGEN® 3-PMH

Effective for the vaccination of healthy cattle, 1 week of age or older against infectious bovine rhinotracheitis (IBR) virus, bovine respiratory syncytial virus (BRSV), parainfluenza 3 virus (PI_3), *Mannheimia haemolytica* and *Pasteurella multocida*.

Features and benefits:

- Only IN vaccine for cattle that protects against bacterial and viral infection
- Demonstrated efficacy – mimics natural exposure to the most common causes of pneumonia for an effective immune response
- Demonstrated Duration of Immunity (DOI)
- IBR – at least 195 days
- BRSV – at least 78 days
- PI_3 – at least 95 days
- *P. multocida* – at least 125 days
- *M. haemolytica* – at least 122 days
- Designed with an IBR that is not temperature-sensitive, ensuring the vaccine will replicate and protect in any situation[3]
- Safe in pregnant cows and in calves nursing pregnant cows
- BluShadow™ diluent helps identify vaccinated animals for confident administration

BOVILIS® NASALGEN® 3

Effective for the vaccination of healthy cattle, 1 week of age or older against infectious bovine rhinotracheitis (IBR) virus, bovine respiratory syncytial virus (BRSV) and parainfluenza 3 virus (PI_3).

Features and benefits

- Demonstrated efficacy – mimics natural exposure to the most common causes of pneumonia for an effective immune response
- Demonstrated Duration of Immunity (DOI)
- IBR – at least 195 days
- BRSV – at least 78 days
- PI_3 – at least 95 days
- Designed with an IBR that is not temperature-sensitive, ensuring the vaccine will replicate and protect in any situation[3]
- Safe in pregnant cows and in calves nursing pregnant cows
- BluShadow™ diluent helps identify vaccinated animals for confident administration

Vaccines should be based on your operation's needs. Work with your veterinarian to determine pathogens of interest and create a protocol for your herd.

BOVILIS® NASALGEN® IP

Effective for the vaccination of healthy cattle 5 months of age or older against infectious bovine rhinotracheitis and parainfluenza 3 viruses.

Features and benefits

- Demonstrated efficacy – mimics natural exposure
- Demonstrated IgA and IgG following intranasal vaccination
- Designed with an IBR that is not temperature-sensitive, ensuring the vaccine will replicate and protect in any situation[3]
- Safe in pregnant cows and in calves nursing pregnant cows

BOVILIS® ONCE PMH® IN

Effective for the vaccination of healthy cattle 1 week of age or older against disease due to *Mannheimia haemolytica* and *Pasteurella multocida*.

Features and benefits:

- Demonstrated safety and efficacy in calves 1 week of age or older

BOVILIS® CORONAVIRUS

An intranasal vaccine that protects calves against enteric disease caused by bovine coronavirus (BCV) – a major cause of diarrhea in young calves and winter dysentery in dairy cows.

Features and benefits:

- Demonstrated efficacy in calves 3 days of age and older
- Demonstrated safety in calves 1 day of age and older

MERCK Animal Health

Intranasal vaccines are just a few of the cattle friendly solutions available from Merck Animal Health.

Find out more at **CattleFriendlyVaccines.com**

Bovilis®

Nasalgen® 3-PMH

Nasalgen® 3

Nasalgen® IP

Once PMH® IN

Bovilis® Coronavirus

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