



# Knowledge

## Arsenal® 4.1 – Effective and Safe Prevention of Bovine Respiratory Disease (BRD)

### SUMMARY

Arsenal® 4.1 is a new modified live vaccine that provides protection against the BVD that's most likely to cause a bovine virus diarrhea (BVD) respiratory outbreak: the noncytopathic (NCP) strain. But Arsenal 4.1 goes beyond that, providing proven respiratory protection against: BVD Type 1 and Type 2, bovine respiratory syncytial virus (BRSV), infectious bovine rhinotracheitis (IBR) and parainfluenza Type 3 (PI<sub>3</sub>).

The efficacy of Arsenal 4.1 has been proven in advanced respiratory challenge models. These efficacy trials used higher viral challenge levels than one may normally experience in the field.

Trial results showed:

- Arsenal 4.1 demonstrated significant protection against BVD Type 2. The BVD Type 2 trial provided a strong challenge, with a 25-percent mortality rate in the group of non-vaccinates.
- Even with a single SubQ dose, Arsenal 4.1 was able to significantly control the clinical signs associated with BRSV.
- Arsenal 4.1 significantly protected against PI<sub>3</sub> in challenge trials as evidenced by significant differences in clinical scores and virus shedding between vaccinated and control calves.

- Arsenal 4.1 demonstrated significant protection against IBR as shown through differences in temperature responses, clinical scores and virus shedding between vaccinated and control calves.
- In all of these challenge trials, Arsenal 4.1 was administered both subcutaneously and intramuscularly. Both routes were found to be equally efficacious. Novartis chose the subcutaneous (SubQ)-only route of administration to be in accordance with Beef Quality Assurance guidelines.
- In field safety studies, Arsenal 4.1 demonstrated outstanding field safety under various commercial field settings and even when used in calves as young as two weeks of age.

Arsenal® 4.1 is labeled for use in healthy non-pregnant cattle as an aid in preventing diseases caused by bovine virus diarrhea (BVD) Types 1 and 2, bovine respiratory syncytial virus (BRSV), infectious bovine rhinotracheitis (IBR) and parainfluenza Type 3 (PI<sub>3</sub>).

Livestock veterinarians and their clients can rest assured of disease protection when using Arsenal 4.1. Its efficacy has

been proven in advanced respiratory challenge models.

Moreover, in field safety studies that exceeded the number of animals the USDA requires, Arsenal 4.1 was found to be safe – even in calves two weeks of age. The details of these challenge and safety trials follow.

### Introduction

In all of the challenge trials that follow, Arsenal 4.1 was administered both subcutaneously and intramuscularly. Both routes were found to be equally efficacious. However, Novartis chose the subcutaneous (SubQ)-only route of administration to be in accordance with Beef Quality Assurance guidelines.

## BVD Type 1 challenge trial

### Protocol

This trial involved 25 yearlings (750 to 1,000 pounds) to determine efficacy of Arsenal 4.1 in preventing BVD Type 1 virus. The animals were randomly assigned into one group each of vaccinates (20 animals) and controls (5 animals). Animals in the vaccinated group received a single 2-mL dose according to

label. At 21 days post-vaccination, all animals received a 4-mL dose of virulent BVD Type 1 USDA-approved challenge intranasally.

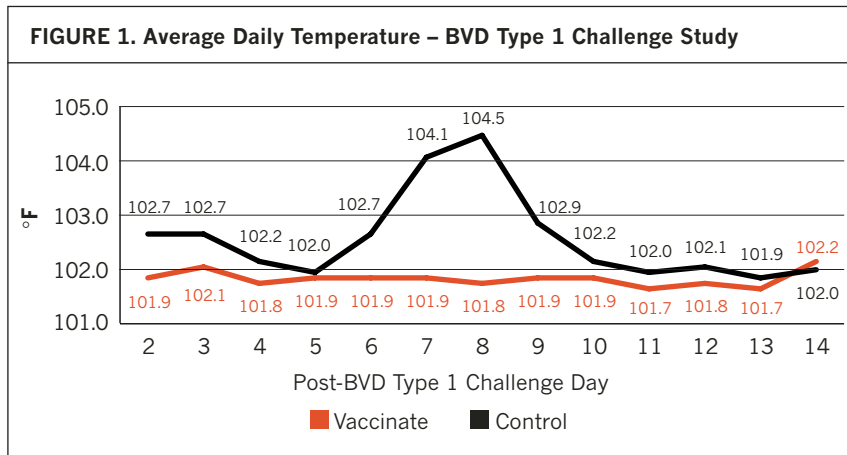
Researchers examined animals daily for clinical signs of respiratory disease. They collected nasal secretions and evaluated body temperature responses starting two days prior to challenge through 14 days post-challenge.

### Results

- Four of the five non-vaccinated animals in the control group demonstrated a febrile response (see Table 1 and Figure 1).
- Three of the five non-vaccinated animals demonstrated clinical signs of BVD (anorexia, diarrhea and ocular discharge).
- Each of the five non-vaccinated animals shed detectable virus for three to five days post-challenge. No detectable virus was shed by any of the vaccinated animals (see Figure 2).
- Four of the five non-vaccinated animals developed leukopenia, a key measure of immunosuppression. No animals in the vaccinated group developed leukopenia.
- All animals in the vaccinated group remained clinically normal.

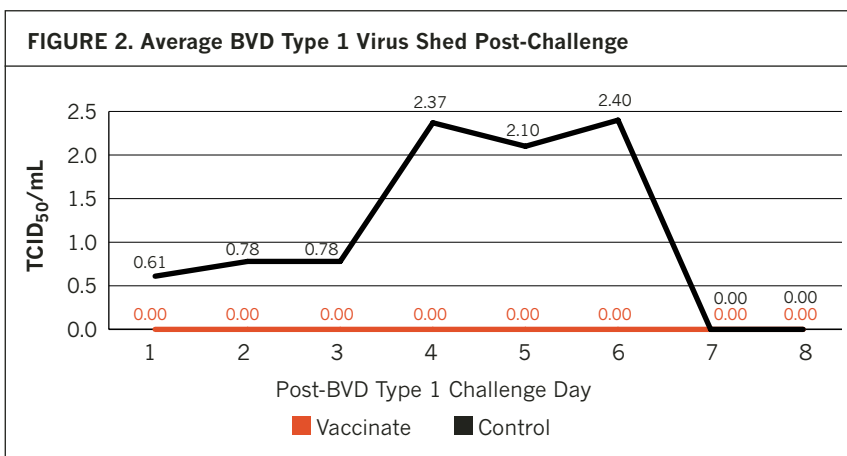
	Number of Animals/Total			
	Temp (≥103.5 F)	Clinical Signs	Leukopenia (Drop in white blood cells)	Virus Shedding
<b>Vaccinate</b>	0/20	0/20	0/20	0/20
<b>Control</b>	4/5	3/5	4/5	5/5
<b>P Value*</b>	0.0004	0.0043	0.0004	<0.0001

\* A p value ≤0.05 is considered statistically significant.



### Conclusion

Researchers concluded that Arsenal 4.1 significantly protected against BVD Type 1 as evidenced by the normal clinical signs, normal temperature, protection against leukopenia and lack of virus shedding in the vaccinated calves.



## BVD Type 2 challenge trial

### Protocol

The trial involved 32 yearlings (750 to 1,000 pounds) to determine efficacy of Arsenal 4.1 in preventing BVD Type 2. The animals were randomly assigned into one group of vaccinates (20 animals) and one control (12 animals) group. Vaccinates received a single 2-mL dose according to label. At 21 days post-vaccination, all animals received a 4-mL dose of virulent BVD Type 2 USDA-approved challenge intranasally.

Researchers examined the animals daily for clinical signs of respiratory disease and body temperature response for 17 days, starting two days prior to challenge through 14 days post-challenge. Nasal secretions were collected daily from each calf beginning two days prior to challenge through post-challenge day 14.

### Results

- Nine of the 12 non-vaccinated control animals exhibited significant signs indicative of BVD. All 12 had clinical signs, 10 exhibited leukopenia, nine developed temperatures greater than 104.5°F and seven shed virus intranasally (see Table 2, Figures 3 and 4).
- Moreover, the challenge was intense enough that three of the non-vaccinated controls died.
- All of the vaccinates survived the post-challenge observation period without developing significant signs of BVD.

### Conclusion

Researchers concluded that Arsenal 4.1 provided significant protection against BVD Type 2 – protection significant enough to protect against BVD-related death.

TABLE 2. BVD Type 2 Efficacy Data

	Number of Animals/Total				
	Temp (≥103.5°F)	Clinical Signs	Mortality	Leukopenia (Drop in white blood cells)	Virus Shedding
Vaccinate	0/20	0/20	0/20	1/20	0/20
Control	9/12	12/12	3/12	10/12	7/12
P Value*	<0.0001	<0.0001	0.0444	<0.0001	0.0002

\* A p value ≤0.05 is considered statistically significant.

FIGURE 3. Average BVD Type 2 Virus Shed Post-Challenge

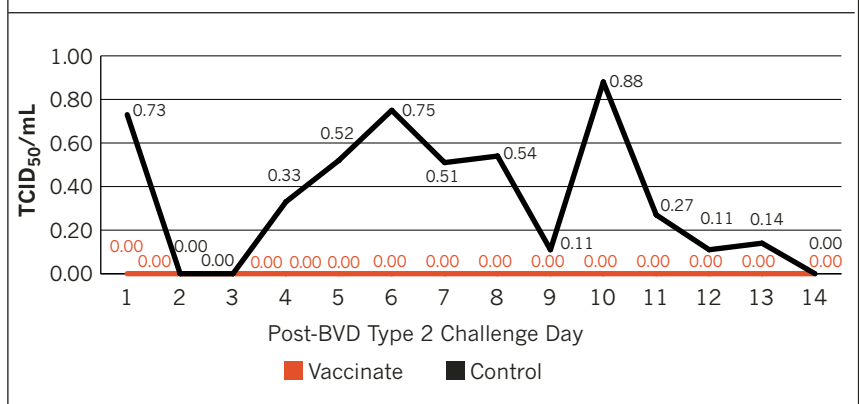
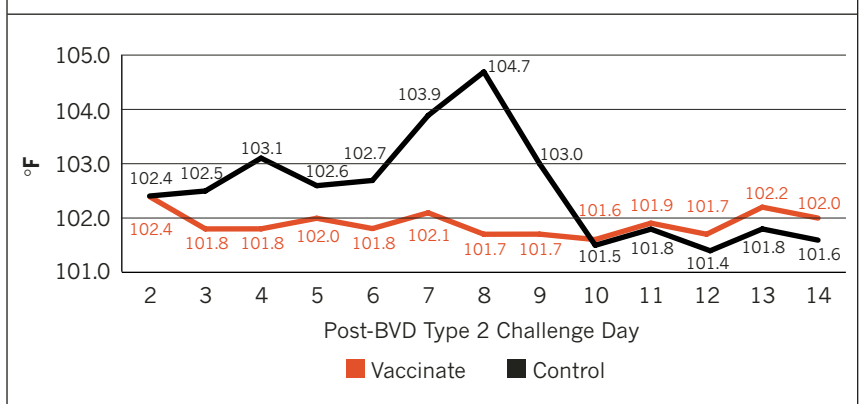


FIGURE 4. Average Daily Temperature – BVD Type 2 Challenge Study



## BRSV challenge trial

### Protocol

The trial involved 34 calves ranging in age from 18 to 36 weeks. The calves were randomly assigned into one group each of vaccinates (22 calves) and controls (12 calves). Animals in the vaccinate group received a single 2-mL dose according to label. At 21 days post-vaccination, all animals received a 4-mL dose of virulent BRSV USDA-approved challenge intranasally.

Researchers examined calves daily for clinical signs of respiratory disease and body temperature response for 17 days, starting two days prior to challenge and through 14 days post-challenge. Nasal secretions were collected daily from each calf beginning two days prior to challenge through post-challenge day 14.

### Results

- The non-vaccinated calves started shedding virus on day two and continued to shed virus through day 14 after challenge (see Figure 5). All non-vaccinated calves shed virus at least one day, and nine of 12 shed virus for at least two consecutive days.
- Only one calf in the vaccinated group shed virus for two or more consecutive days.
- Nine out of the 12 non-vaccinated calves exhibited clinical signs indicative of BRSV virus (see Table 3 and Figure 6).
- More than 90 percent of the vaccinates survived the post-vaccination period without developing significant signs of BRSV infection.

### Conclusion

Researchers concluded that Arsenal 4.1 significantly protected against BRSV as evidenced by the normal clinical signs and low level of virus shedding. Results were equal between vaccinates that received a single, SubQ dose vs. a single intramuscular dose of Arsenal 4.1

TABLE 3. BRSV Efficacy Data

	Clinical Signs	Virus Shedding
<b>Vaccinate</b>	2/22	1/22
<b>Control</b>	9/12	9/12
<b>P Value*</b>	0.0002	<0.0001

\* A p value  $\leq 0.05$  is considered statistically significant.

FIGURE 5. Average BRSV Virus Shed Post-Challenge

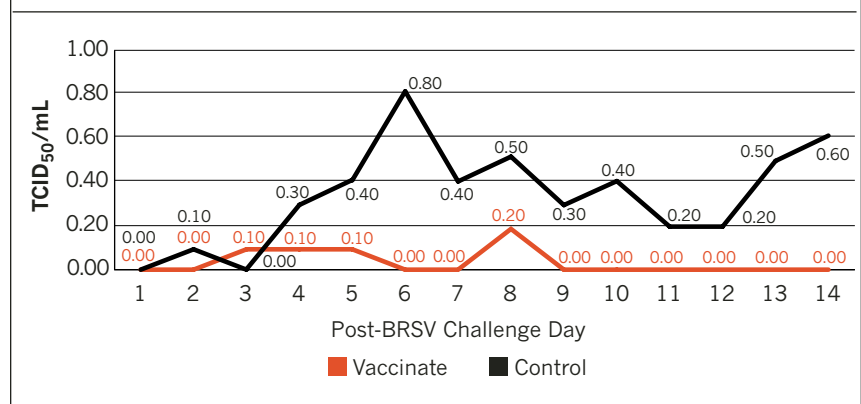
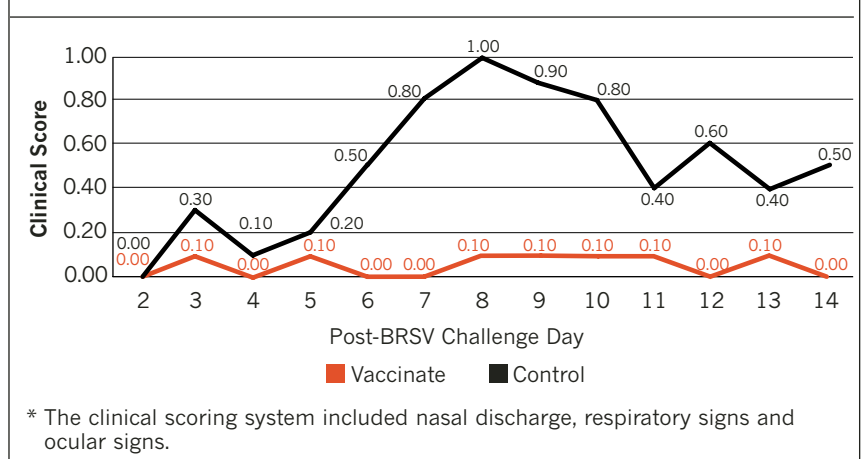


FIGURE 6. Average Daily Total Clinical Score\* – BRSV Challenge Study



## IBR challenge trial

### Protocol

Researchers conducted a trial involving 38 yearlings (700 to 900 pounds) to determine efficacy of Arsenal 4.1 in preventing IBR. Animals were randomly assigned into a vaccinated group (20 animals) and a non-vaccinated group (18 animals). Animals in the vaccinated group were administered a single 2-mL dose according to label. At 23 days post-vaccination, all animals received a 4-mL dose of virulent IBR USDA-approved challenge intranasally.

Researchers examined the yearlings daily for clinical signs of respiratory disease and collected nasal secretions. Each yearling received a clinical score based on severity of respiratory signs. Researchers also recorded body temperatures for 17 days starting two days prior to challenge.

### Results

- None of the vaccinated animals had temperatures greater than 103.5°F post-challenge, while all of the control animals had temperatures over 103.5°F for two to seven days post-challenge (see Table 4 and Figure 7).
- Vaccinated animals had an average total clinical score of 0.05, while the non-vaccinated controls had an average total clinical score of 30.67 (see Figure 8).
- All of the control animals shed virus for at least five days (see Figure 9). Of the 20 vaccinates, only one shed virus.

### Conclusion

Researchers concluded that Arsenal 4.1 significantly protected against IBR. This was proven by demonstrating significant differences in temperature responses, clinical scores and virus shedding between the vaccinated and control calves.

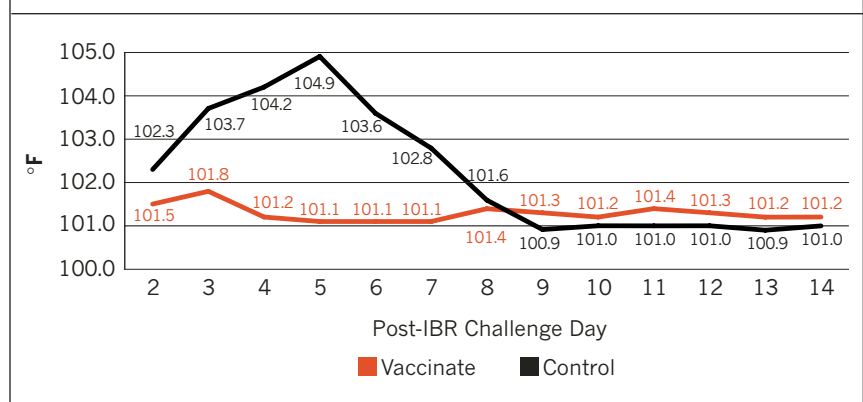
**TABLE 4. IBR Efficacy Data**

	Total Average Clinical Score**	Temp ( $\geq 103.5^{\circ}\text{F}$ ) Number of Animals/Total	Virus Shedding Number of Animals/Total
<b>Vaccinate</b>	0.05	0/20	1/20
<b>Control</b>	30.67	18/18	18/18
<b>P Value*</b>	<0.0001	<0.0001	<0.0001

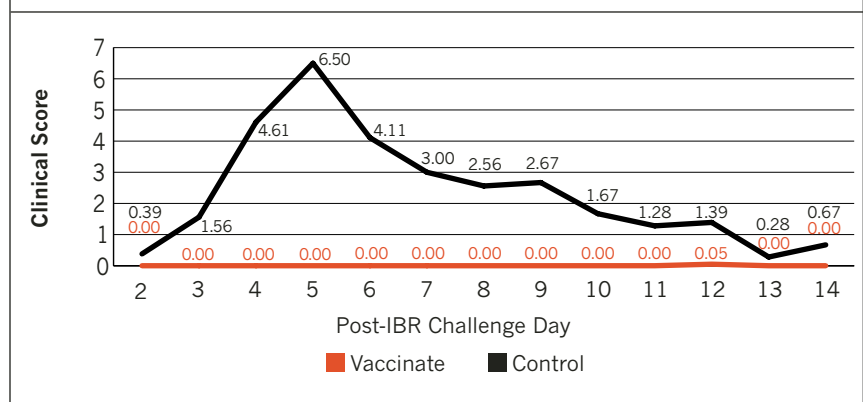
\* A p value  $\leq 0.05$  is considered statistically significant.

\*\* The clinical scoring system included nasal discharge, respiratory signs, ocular signs and anorexia.

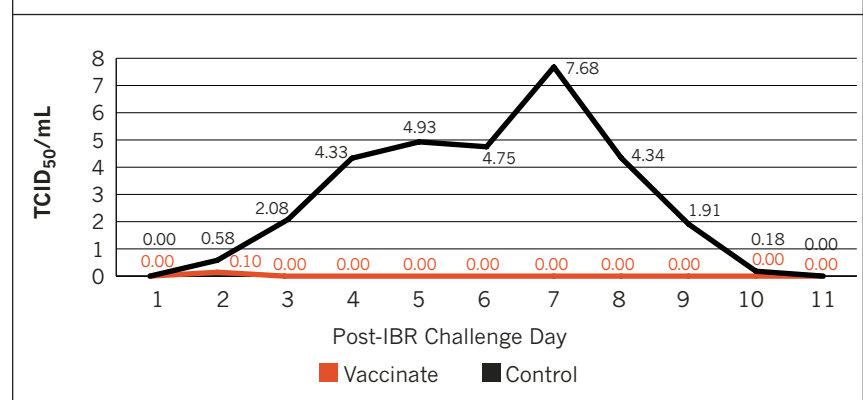
**FIGURE 7. Average Daily Temperature – IBR Challenge Study**



**FIGURE 8. Average Daily Total Clinical Score**



**FIGURE 9. Average IBR Virus Shed Post-Challenge**



	Total Average Clinical Score**/Group
Vaccinate	2.80
Control	6.27
P Value*	0.0056

\* A p value ≤0.05 is considered statistically significant.  
 \*\* The clinical scoring system included nasal discharge, ocular signs and anorexia.

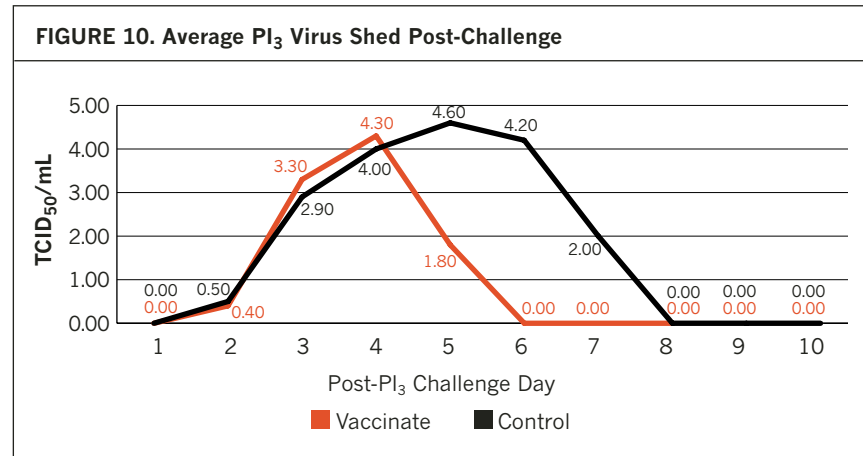
## PI<sub>3</sub> challenge trial

The trial involved 31 calves (350 to 500 pounds) to determine efficacy of Arsenal 4.1 in preventing PI<sub>3</sub>. The calves were randomly assigned into a vaccinated (20 calves) and a control (11 calves) group. Prior to vaccination, nasal specimens were collected from calves in both groups. Animals in the vaccinated group received a single 2-mL dose of Arsenal 4.1. At 21 days post-vaccination, all animals received a 4-mL dose of virulent PI<sub>3</sub> USDA-approved challenge intranasally.

Researchers examined calves daily for signs of clinical disease and body temperature response for each of the 14 consecutive days post-challenge. Nasal secretions were collected daily from each calf beginning two days prior to challenge through post-challenge day 14.

## Results

- Vaccinated calves had significantly lower total clinical scores ( $p = 0.0056$ ) when compared to the control group (See Table 5).
- Over the 14-day challenge period, vaccinated calves shed significantly less virus than non-vaccinates ( $p = 0.0005$ ) (see Figure 10).



## Conclusion

Researchers concluded that Arsenal 4.1 significantly protected against PI<sub>3</sub> as evidenced by significant differences in total clinical scores and virus shedding between the vaccinated and control calves.

## Field safety testing

### Protocol

Arsenal 4.1 also has undergone vigorous safety testing. The trials were conducted on:

- A commercial dairy in Kansas with 215, two-week-old Holstein calves
- A commercial feedlot in Texas with 291, 500-pound beef calves
- A veal operation in Ohio with 353, three-month-old Holstein calves

Veterinarians vaccinated the calves according to protocol and label directions. Calves received a single 2-mL subcutaneous dose of Arsenal 4.1.

## Results

There were only two minor vaccine-related adverse events (0.2% reaction rate) involving minor swelling at the injection site, which resolved in a week or less. Arsenal 4.1 was found to be safe in a wide range of

operations, including a veal operation, commercial dairy and a beef feedlot.

## Conclusion

This trial data supports the safety of Arsenal 4.1 when administered under field conditions as a single 2-mL subcutaneous dose. Furthermore, it shows that Arsenal 4.1 is safe for use in calves at two weeks of age or older.

## Summary

- Overall, these trials used higher viral challenge levels than one may normally experience in the field.
- Arsenal 4.1 demonstrated its ability to withstand respiratory challenge due to BVD Types 1 and 2, BRSV, IBR and PI<sub>3</sub>.
- Arsenal 4.1 showed significant protection against BVD Type 2. The BVD Type 2 trial provided a strong challenge, with a 25-percent mortality rate in the group of non-vaccinates.
- Even with a single SubQ dose, Arsenal 4.1 was able to significantly control the clinical signs associated with BRSV.
- Arsenal 4.1 demonstrated outstanding field safety under various commercial field settings and even when used in calves as young as two weeks of age.

