Nasalgen® 3

TECH BULLETIN

MERCK Animal Health

Key Highlights

- Results of this study demonstrate protective efficacy for the IBR viral fraction of Nasalgen 3 and no interference by the other two antigens in N3 after one intranasal administration to calves 4 to 7 days old.
- N3 resulted in significantly lower incidence and duration of clinical IBR (including rectal temperature), as well as lower magnitude and duration of nasal shedding of IBR virus.
- Results of this study support the claim that N3 is safe and effective for intranasal vaccination of healthy calves at 1 week of age or older against respiratory disease caused by IBR virus.

Efficacy of the Infectious Bovine Rhinotracheitis Fraction of Nasalgen® 3 in Calves 4 to 7 Days Old

SUMMARY

Nasalgen® 3 (N3) has been shown to be effective for vaccination of healthy cattle, 1 week of age or older, against Infectious Bovine Rhinotracheitis (IBR) virus, Bovine Respiratory Syncytial Virus (BRSV) and Parainfluenza 3 (PI_3) virus that are pathogens implicated in the Bovine Respiratory Disease (BRD) complex. Nasalgen 3 is safe for use in pregnant cows and in calves nursing pregnant cows. For this study, 46 colostrum-deprived Holstein calves were randomly assigned to be vaccinated intranasally with one dose of N3 (23 head) that contained the minimum protective dose of IBR or a placebo vaccine (23 head) that did not contain the IBR fraction but contained the other viral antigens in N3. All calves were 4 to 7 days old on the day of vaccination (Day 0). No adverse reactions were observed after vaccination. All calves were commingled prior to challenge and on Day 29 were challenged by intranasal administration of virulent IBR virus. A significantly ($P<0.0001$) lower proportion of the calves in the N3 group (22.7%) developed clinical IBR than those in the control group (100%). A significantly ($P=0.0002$) lower proportion of the calves in the N3 group (18.2%) developed fever than in the control group (77.3%). Duration of clinical IBR was significantly ($P<0.0001$) shorter for calves vaccinated with N3 than for those in the control group. Maximum titers (Log_{10} $TCID_{50}$/mL) of IBR virus shed in nasal secretions were significantly ($P<0.0001$) lower for calves vaccinated with N3 than for calves in the control group. The duration of nasal shedding of IBR virus was significantly ($P=0.0001$) shorter for calves vaccinated with N3 than for those in the control group. Nasalgen 3 provided protection to calves 4 to 7 days of age, as reflected by the lower proportion of calves with clinical IBR and/or fever, by shorter duration of clinical IBR, by lower maximum titers and by shorter duration of nasal shedding of IBR virus after challenge.

INTRODUCTION

Nasalgen 3 (N3) vaccine has been developed by Merck Animal Health for intranasal administration against viral pathogens known to be causal in the Bovine Respiratory Disease complex. N3 contains modified live viruses (Infectious Bovine Rhinotracheitis [IBR] virus, Bovine Parainfluenza 3 [PI_3] virus and Bovine Respiratory Syncytial Virus [BRSV]). This technical bulletin reports the results of research that demonstrate protective efficacy for the IBR viral fraction of N3 and no interference by the other two antigens in N3 after one intranasal administration to calves 4 to 7 days old.

EXPERIMENTAL PROCEDURES

Forty-six Holstein calves (27 males, 19 females) were obtained from a single source, identified by unique individual numbers, deprived of colostrum and transported (two shipments) to the study site at De Soto, KS. Prior to arrival, the calves were randomly assigned to be vaccinated intranasally (IN) with N3 or with a placebo vaccine (control group). Calves were housed in individual hutches that were segregated by treatment group and were physically separated by at least 15 feet. Each calf was bottle-fed (until able to be fed with a bucket) at least 2 quarts of milk replacer twice daily and had access *ad libitum* to fresh water and to a calf starter diet. Calves were allowed 4 to 5 days to acclimate prior to enrollment. Health care was managed by the attending veterinarians. All calves were confirmed "negative" (antigen-capture Enzyme-Linked Immunosorbant Assay) for persistent infection with Bovine Viral Diarrhea Virus (BVDV).

All calves were 4 to 7 days old on the day of vaccination (Day 0). Nasalgen 3 was prepared so that the dose administered contained the minimum protective dose (MPD) of IBR virus and contained PI_3 virus and BRSV at or above titers licensed for release. The placebo vaccine contained the same antigens as N3 but without the IBR fraction. One mL of placebo vaccine was administered into each nostril of 23 calves and one mL of N3 was administered into each nostril of 23 calves.

Four days prior to challenge with virulent IBR virus, all calves were commingled. On Day 29, 44 calves were challenged IN with virulent Cooper strain IBR virus. All calves were monitored daily from Day 28 to Day 46 (Day -1 to Day 17 post-challenge) for clinical signs of disease. The rectal temperature of each animal was recorded daily from Day 28 through Day 43 (Day -1 to Day 14 post-challenge). Serum was collected on Days 36 and 43, and nasal secretions were sampled daily from Day 30 through Day 46.

The experimental unit was the individual calf. Primary outcome variables were the proportion of calves affected with acute morbidity and fever. Supporting variables were nasal shedding of IBR virus post-challenge and duration of acute morbidity post-challenge. The supporting variables were subjected to exploratory analyses. Titers of SN antibody to IBR virus were used as an enrollment criterion ("negative"), as an indicator of biosecurity ("negative") and as a general indicator of antigenic/immunologic response ("positive") to vaccination and/or to challenge. Those SN titers were not quantitated for statistical analyses. Personnel who administered the challenge, performed clinical observations and/or performed laboratory procedures were blinded to the treatment group to which a calf was allocated.

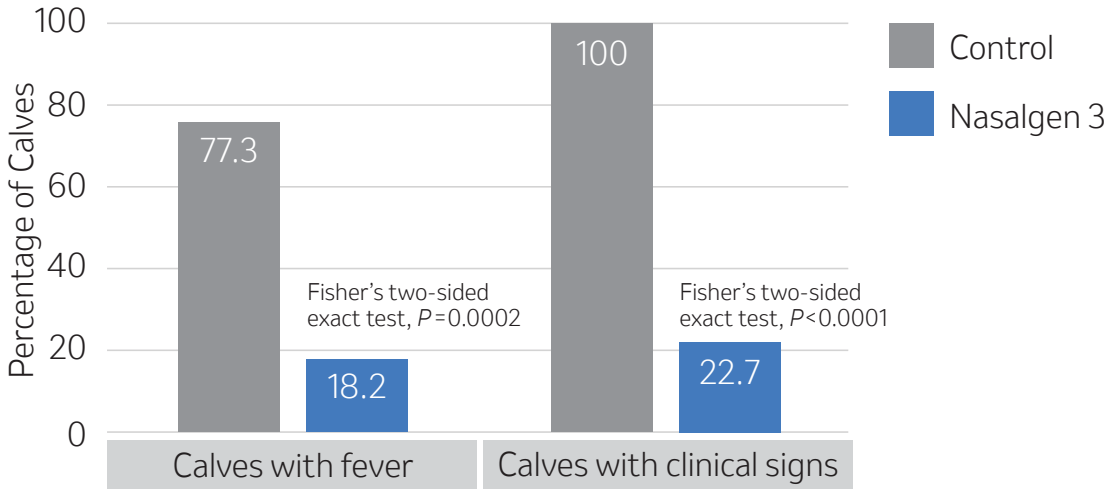
RESULTS

No adverse events attributable to the vaccine were observed. During the post-vaccination period, one calf (male) in the N3 group died, and one calf (male) in the control group was euthanized for humane reasons. Conclusions of necropsy findings were that the condition of each calf was unrelated to vaccination. A few additional calves were transiently affected by conditions that resolved after prescribed treatment that were not related to vaccination and that did not influence the outcome of the study.

All calves were seronegative (SN ≤ 1:2) to IBR virus prior to enrollment and all calves in the control group remained seronegative until Day 43 (Day 14 post-challenge). Calves vaccinated with N3 responded serologically and demonstrated an anamnestic response post-challenge.

After challenge, the proportion of calves that developed clinical IBR in the N3 group (5/22, 22.7%) was significantly (Fisher's two-sided exact test, $P<0.0001$) lower than that proportion in the control group (22/22, 100%, Figure 1). Clinical signs consisted primarily of moderate to severe nasal discharge, nasal lesions, depression and dyspnea. Fever was defined as rectal temperature ≥ 104.0°F for two or more consecutive days post-challenge. The proportion of calves with fever was significantly (Fisher's two-sided exact test, $P=0.0002$) lower for calves in the N3 group (4/22, 18.2%) than for calves in the control group (17/22, 77.3%, Figure 1).

Figure 1. Proportion of calves with fever and other clinical signs of IBR after challenge.



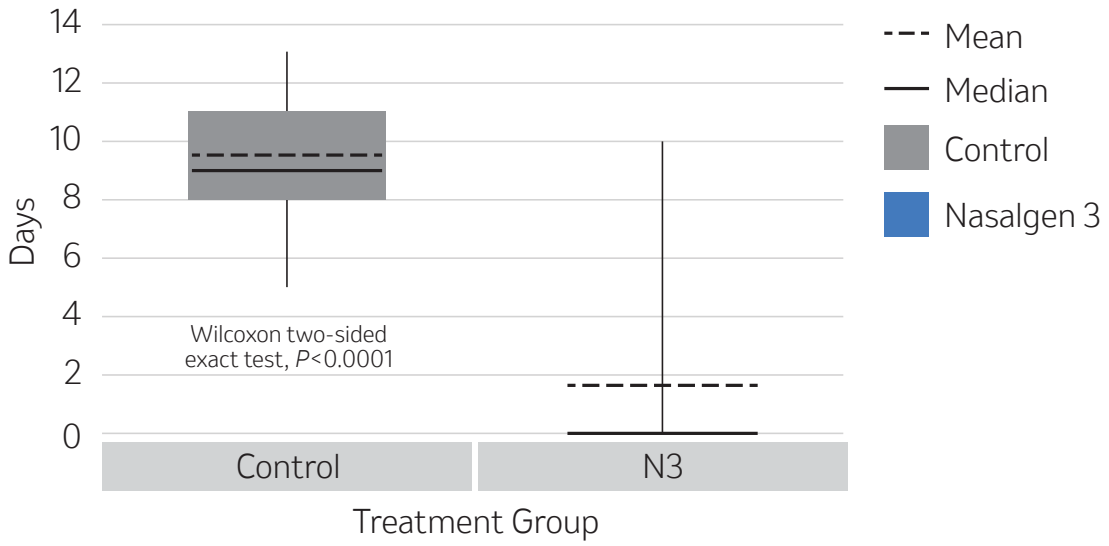
The mean maximum rectal temperature for calves in the N3 group was 103.1°F and for those in the control group was 104.7°F. The mean duration of fever, including any post-challenge day with a rectal temperature ≥ 104.0°F, was 0.6 days for calves in the N3 group and 3.4 days for calves in the control group.

After challenge, the duration of IBR morbidity was significantly (Wilcoxon two-sided exact test, $P<0.0001$) shorter for calves vaccinated with N3 than for calves in the control group (Table 1, Figure 2).

Table 1. Quartile summary for duration of IBR morbidity post-challenge.

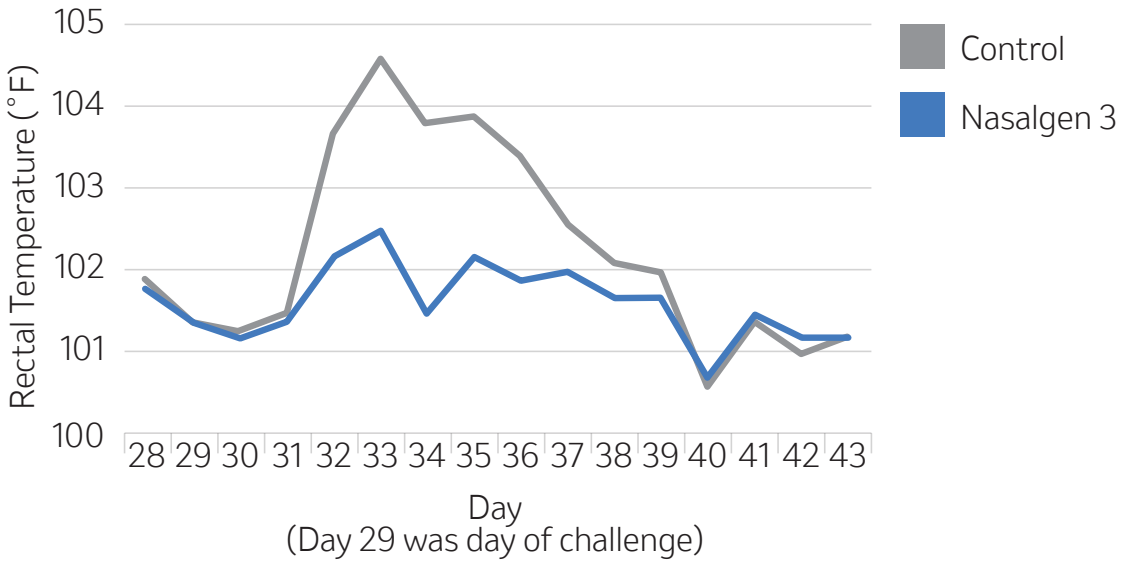
TREATMENT GROUP	*N*	MEAN	MINIMUM	LOWER QUARTILE	MEDIAN	UPPER QUARTILE	MAXIMUM
CONTROL	22	9.4	5	8	9	11	13
N3	22	1.8	0	0	0	0	10

Figure 2. Duration of IBR morbidity post-challenge.



The mean rectal temperatures (°F) of calves in each treatment group by day of study from day 28 through day 43 are presented in Figure 3.

Figure 3. Mean rectal temperatures (°F) of calves in each treatment group by day of study. Intranasal challenge with virulent IBR virus was on Day 29.

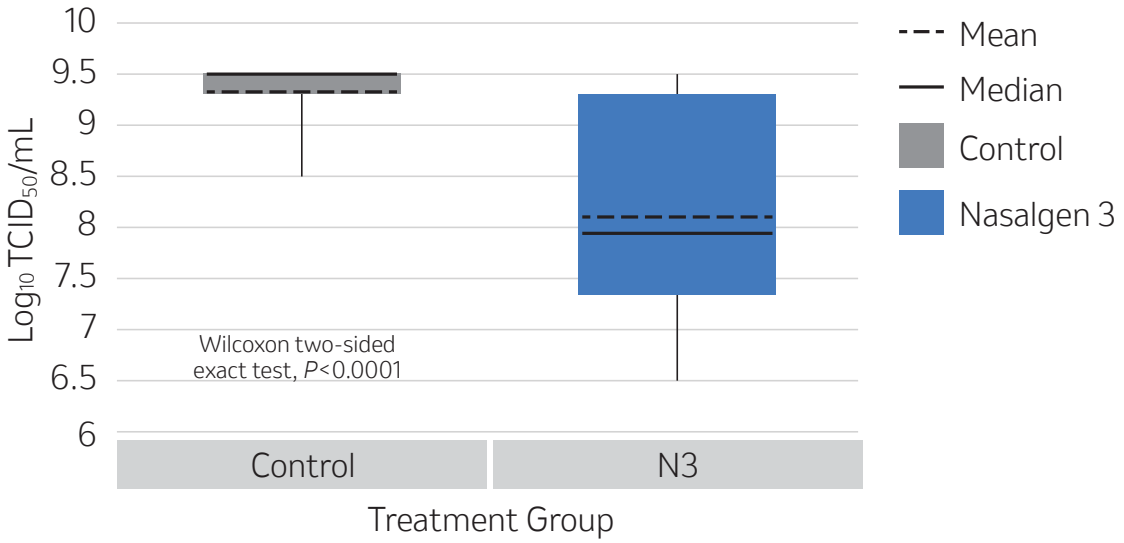


On Day 28 (one day before challenge), none of the calves shed IBR virus in nasal secretions. All calves in each group shed IBR virus in nasal secretions following challenge. Maximum titers (Log_{10} $TCID_{50}$/mL) of IBR virus shed in nasal secretions were significantly (Wilcoxon two-sided exact test, $P<0.0001$) different for calves in the control group and those in the N3 group (Table 2, Figure 4).

Table 2. Maximum titers (Log_{10} $TCID_{50}$/mL) of IBR virus shed in nasal secretions (Wilcoxon two-sided exact test, $P<0.0001$).

TREATMENT GROUP	*N*	MEAN	MINIMUM	LOWER QUARTILE	MEDIAN	UPPER QUARTILE	MAXIMUM
CONTROL	22	9.36	8.5	9.3	9.5	9.5	9.5
N3	22	8.1	6.5	7.3	7.9	9.3	9.5

Figure 4. Maximum titers (Log_{10} $TCID_{50}$/mL) of IBR virus shed in nasal secretions by treatment group.

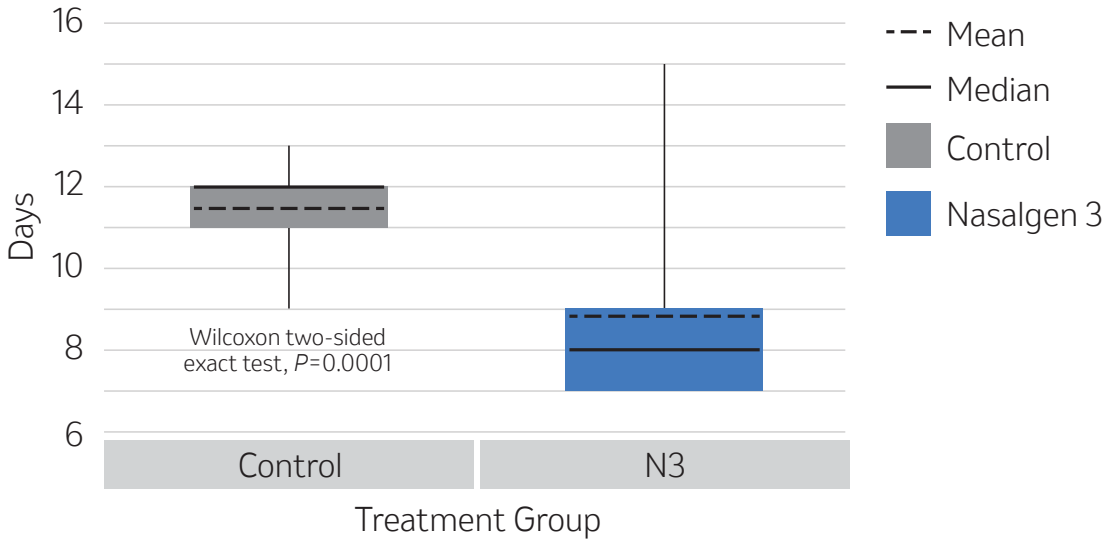


The duration of nasal shedding for calves in the N3 group was significantly (Wilcoxon two-sided exact test, $P=0.0001$) shorter than that for calves in the control group (Table 3, Figure 5).

Table 3. Quartile summary of analysis for duration of nasal shedding of IBR virus post-challenge.

TREATMENT GROUP	*N*	MEAN	MINIMUM	LOWER QUARTILE	MEDIAN	UPPER QUARTILE	MAXIMUM
CONTROL	22	11.5	9	11	12	12	13
N3	22	8.8	7	7	8	9	15

Figure 5. Duration of nasal shedding of IBR virus after challenge with virulent IBR virus.



DISCUSSION

The serologic responses were evidence of the biosecurity of the facility and study design, of the antigenic/immunologic effect of N3 and of the challenge virus used in this study. The lower proportion of calves that developed clinical IBR and the shorter duration of clinical signs (including fever) of IBR for those calves vaccinated with Nasalgen 3 demonstrate the ability of this vaccine to protect neonatal, colostrum-deprived calves. Further, the lower magnitude (approximate 1.3 Log_{10}) and shorter duration (2.7 days) of post-challenge nasal shedding of IBR virus are hallmarks of protection and have important implications for horizontal exposure during a herd outbreak.

CONCLUSIONS

Results of this study demonstrate protective efficacy of the IBR viral fraction of Nasalgen 3 and confirmed the non-interference by the other antigenic fractions in Nasalgen 3 when a single dose with the minimum protective dose of the IBR viral fraction was administered intranasally to healthy calves 4 to 7 days old. Nasalgen 3 resulted in significantly lower incidence and duration of clinical IBR (including rectal temperature), as well as lower magnitude and duration of nasal shedding of IBR virus.

Results of this study support the claim that Nasalgen 3 is safe and effective for intranasal vaccination of healthy calves at 1 week of age or older against respiratory disease caused by IBR virus.

REFERENCES

Data on file: USDA-approved efficacy report for N3.

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US-NAL-200200004

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