Common Questions and Answers on *MAXI/GUARD* Nasal Vac

***Bordetella bronchiseptica* Avirulent Live Culture Vaccine (Code 1081.00)**

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Abstract: *Neonatal bordetellosis in baby pigs leads to subtle damage to the ciliary brush border which is intimately involved in physical cleansing of the nasal epithelium and the ciliated pulmonary tree. These desquamation lesions in the ciliary layer allow other pathogens, such as Pasteurella multocida Type D, to gain a foothold potentially resulting in severe nasal and pulmonary pathology. Application of a nontoxigenic strain of Bordetella bronchiseptica during early life leads to colonization and protection of the ciliary layer through competitive exclusion of pathogens. Some cross protection for Strep. suis has been reported and protection of the respiratory system in a general way is valuable in reducing incidence of PRDC . This technology (mucosal ciliary receptor saturation) offers the veterinarian and production manager a unique tool in the fight to control respiratory disease in intensive swine units, decrease labor costs, decrease antibiotic usage, decrease production times, and increase profits.*

1) What is PRDC?

The **porcine respiratory disease complex** (**PRDC**) is a multi-factorial problem involving environment (hygiene and air quality: ammonia levels, ventilation, dust levels), animal stocking densities, acquired immunity, innate genetic-based resistance, and routine challenge by endemic organisms frequently co-existing in one host. Organisms routinely recovered from swine lung includes *B. bronchiseptica, P. multocida, Strep. suis, Hemophilus parasuis, Actinobacillus pleuropneumoniae, Salmonella sp., M. hyopneumoniae, PRRSV, Swine Influenza Virus, Porcine Circovirus, and Porcine Pseudorabies Virus*. While many porcine disease problems have been eliminated or brought under control through progressive farm management practices (multi-site production, AIAO, medicated early weaning, age segregation, feeding sub-therapeutic levels of antibiotics, injecting antibiotics in a preventive mode termed metaphylaxis, farm biosecurity, immunization programs, newer generation veterinary therapeutics/treatments, nutrition, genetics), swine respiratory disease incidence has remained fairly constant over the past 20 years. PRDC costs the U.S. swine industry approximately $210 million per annum.

2) What is the 18 week wall experienced in finish units?

Despite space-age facility engineering, genetic advancement, sophisticated management, extensive record keeping and analysis (PigCHAMP, etc.), and epidemiological disease studies, the PRDC problem continues to persist. Pigs on finishing floors regularly hit an invisible 16-18 week wall involving pulmonary disease and stagnant weight gains. Combinations of 2-3 agents (co-pathogens) are common, such as PRRSV combined with SIV, PCV, M. hyo, A. pleuro, or Pasteurella pneumonia. A percentage of finish pigs may also experience acute death from systemic *Streptococcus suis* meningitis. This is extremely costly. The 18 week wall may cost the swine producer an additional ten days in production time and increased costs in treating

respiratory diseases.

3) What is *Bordetella bronchiseptica* and how common is Bordetellosis in swine?

Bordetella bronchiseptica (Bb), a small gram-negative motile cocco-bacillus, is fairly ubiquitous in the animal kingdom. A total of 113 strains from 11 different host species have been identified. Approximately 88% of swine isolates have ribotype 3 DNA gel patterns while a few swine isolates are ribotype 2. Ninety-nine percent of swine Bb isolates examined by USDA ARS (NADC, Ames, IO) have been either ribotype 2 or 3 (communication from Ms. Karen Register, July 3, 2000). Bordetellosis in swine takes two forms, neonatal and adult. Pulmonary bordetellosis (whooping cough) occasionally occurs in nursing or recently weaned piglets. Atrophic rhinitis (AR) is the outcome in middle age or older animals if severe chronic disease exists. **The AR syndrome can be regressive (Bb toxin-induced; NPAR) or progressive (Pm becomes involved too; PAR).** The adult form of AR is obvious from the anatomical deviations but is generally considered a low grade threat today by U.S. producers and veterinarians alike. Few twisted or thickened snouts with blown-out turbinates are regularly observed in the U.S. today but the organism (Bb) continues to persist in 97.7% of herds (1994 Elanco Animal Health Total Respiratory Analysis and Control or TRAC Study) surveyed at slaughter. **Damage from Bb can be less obvious than AR and the threat more insidious resulting in an underlying predisposition for more significant respiratory disease problems at an older age. Neonatal bordetellosis (NB) should not be discounted as insignificant because it can lead to costly respiratory disease problems. It is more common than realized because the lesions are subtle and frequently just microscopic.**

4) What is Nasal Vac?

MAXI/GUARD Nasal Vac is a modified live, feline derived, nontoxigenic, *Bordetella bronchiseptica* intranasal vaccine that easily colonizes the ciliated epithelium of the turbinates. The vaccine should be administered within the first three days of life, 2 cc per nostril. Nasal Vac attaches to and colonizes the healthy ciliated respiratory epithelium (brush border) serving as a competitive inhibitor, thus effectively excluding or blocking the attachment of toxigenic Bordetella strains and preventing the early damage that leads to severe respiratory disease in growing pigs. Bordetella is known to produce adhesin proteins which aids attachment of itself and other bacteria to respiratory mucus and cilia. Nasal Vac organisms essentially fill up the parking spaces (glycolipid receptor cell sites for adhesins) for attachment by pathogenic Bordetella, and putatively *Haemophilus parasuis, Streptococcus suis and P. multocida.* This preserves the ciliary layer important for physical clearance of dust and pathogens trapped in the mucous covering. Protection from Hps, APP (pleuropneumonia) and *Mycoplasma hyopneumoniae* may also be implied by protecting this physical mucociliary apparatus.

5) How is Nasal Vac administered?

Nasal Vac is administered intranasally (0.5 ml/nostril) during the first 1-3 days of life where it quickly colonizes the nasal turbinate and respiratory (tracheal, bronchial) ciliated

epithelium. Colonization by a competitive blocker organism is important during the first 21 days of life as this is a critical period for damage to the mucociliary apparatus by pathogenic Bordetella. Natural infection by Pm resulting in severe AR increases between 12-16 weeks in unprotected animals. Nasal tips are provided with the vaccine. One of these tips is attached to a specialized fixed-dose syringe to enable direct application into the nasal cavity. The vaccine is delivered as a liquid stream directly into the nasal cavity while the piglet is held upright with the head and nose projected upward.

6) How does Nasal Vac protect or work?

Nasal Vac attaches to the ciliated turbinate epithelium and helps stimulate a secretory IgA response. Nasal Vac occupies Bb attachment sites thus effectively blocking attachment of pathogenic Bb. **By preventing attachment of pathogenic Bb we help preserve the integrity of the ciliated epithelium. The ciliated respiratory epithelium is the primary filter for the upper respiratory tract. Properly filtered air greatly decreases the pig's pulmonary challenge from particulate matter and air-born pathogens, such as P. multocida and Strep. suis.**

The vaccinal strain acts mainly through blocking attachment of pathogenic Bordetella. After 21 days of age, presence of the competing vaccinal strain is less critical, perhaps due to IgA development. This organism attaches to cilia near the lumen of the respiratory tree, rather than invading deeper tissues. Attachment is dependent upon protein adhesins produced by the organism. Successful colonization of the piglet's ciliated epithelium leaves us to believe that there is no maternal interference even if the sow has IgG antibodies to Bordetella, as these antibodies are not secreted into the lumen of the piglet's respiratory tract. Bordetella bronchiseptica also stimulates the immune system in a general way, thus any antigen swallowed or taken up into the respiratory lymph nodes may provide a generalized secondary boost to the immune system. Some producers have stated they use Nasal Vac primarily because 'it puts a bloom on their piglets.'

7) Will Nasal Vac protect against rhinitis (clinical or subclinical)?

Yes. Nasal Vac is effective in Progressive Atrophic Rhinitis (PAR) and non-PAR Bordetella herds. However, this is not the main reason to administer this product. Generalized protection for the ciliated respiratory tree is the key motivation to use Nasal Vac.

8) Can Nasal Vac be used concurrently with premedication (antibiotics or medicated milk replacer) in baby pigs?

Yes. There is reason to suspect that concurrent use of antibiotics and live bacterial vaccines may be defeating the purpose of a given vaccination program and wasting live vaccine. Practically we have not observed this problem with Nasal Vac. Through selection of antibiotics for which the vaccine is resistant, any suspicion of negative interaction between antibiotic and vaccine can be eliminated. The location of our Nasal Vac organisms post-exposure also has implications for any antibiotic effect **as few systemically applied antibiotics reach significant levels at the attachment locale of the vaccinal**

organisms (i.e., the mucociliary layer). Newer generation antibiotics, such as Baytril (enrofloxacin), Nuflor (florfenicol), and Naxcel (ceftiofur) are unique as they will reach MIC or effective levels in the lung parenchyma and in the mucociliary layer. This makes these antibiotics more useful in effectively treating respiratory disease. Prior generation antibiotics such as tetracycline or penicillin generally failed to reach inhibitory levels out in the ciliated mucous layer of the respiratory tree. Our vaccinal strain also has a resistant pattern against seven antibiotics (Ampicillin, Apramycin, Ceftiofur, Clindamycin/Pirlimycin, Penicillin G, Spectinomycin, and Streptomycin). This knowledge allows the veterinarian or herdsmen to select from this list of antibiotics to treat endemic disease during the first two weeks without risk of interfering with Nasal Vac colonization. Judicious antibiotic selection requires that the treated disease agent (or organism) be susceptible to these agents, i.e. susceptibility testing. A good example is *Strep. suis* swollen joints in baby pigs during the first week of life. Either Penicillin G or ceftiofur (Naxcel/Excenel) would be acceptable approaches here in the U.S. and neither would interfere with the Nasal Vac vaccine. During 1999, Addison Labs completed a concurrent Excenel (ceftiofur, 50 mg/ml, 0.1 ml i.m., Pharmacia & Upjohn) and Nasal Vac exposure study in conventional neonatal swine in mid-Missouri. Our avirulant *Bordetella bronchiseptica* vaccinal organism was cultured from the nasal cavity of 10 of 10 piglets on day 11 (8 days after exposure) from two ceftiofur treated litters (5 randomly chosen from each litter). In addition to Excenel, two of these piglets were also treated daily with intramuscular penicillin for swollen joints (presumably *Strep. suis*). Earlier in-house studies showed Nasal Vac compatibility with injectable oxytetracycline (LA200) co-administration to baby pigs.

9) Will Nasal Vac reduce my antibiotic demand?

Yes. Protected vaccinates should not require antibiotic therapy for respiratory conditions as often as effected non-vaccinates, especially after weaning. Recent reports from Mexico indicate that $3,000 in antibiotic costs for respiratory diseases was saved for one herd after Nasal Vac administration.

10) Once Nasal Vac is administered, can other respiratory disease vaccines be reduced or dropped from the herd?

Our experience suggests that Nasal Vac is not a stand alone approach to disease prevention. Initially, other products may be required. Over time herds may gradually be weaned off some of these products to some degree. Repeated field reports indicate that traditional vaccine usage can be reduced over time. Sow vaccination programs are generally unaffected.

11) What is the PumpIt vaccinator?

Addison Labs stocks a fixed dose (0.5 ml) syringe/vaccinator which was developed to expedite intranasal delivery.

12) How is Nasal Vac packaged?

For the US and Mexican market, Nasal Vac is packaged in 30 ml (30 dose) rubber stoppered plastic bottles, packed six per box, two boxes (12 bottles) shrink wrapped per unit of issue. Disposable plastic syringe nasal tips are

provided along with vaccine. A special order 10 dose vial is currently available for certain international locales where herds are smaller. The label is currently offered in English, although special requests for other languages will be considered when adequate volumes are desired. Addison Labs has applied for APHIS approval to market a 10 dose vial of Nasal Vac in the U.S. Fifty or 100 dose vials can be made available by special request.

13) How should Nasal Vac be handled?

Handling the product requires reasonable care as refrigeration is indicated (but not frozen). Unused quantities should be placed back into the refrigerator where possible. Practically at room temperature in the farrowing house, the product will last for several days, as long as freezing, extreme heat, and gross contamination are avoided.

14) What is unique about the organism used in Nasal Vac vaccine?

The vaccinal strain produces adhesion proteins but no toxins or pathogenicity. Normally adhesions are associated with pathogenicity. J. Bruce Addison ran the Missouri Bordetellosis Reference Laboratory for many years and Nasal Vac is one of the many Bordetella isolates which were recovered. It came from the resident Missouri feline population. After proprietary laboratory manipulation, Nasal Vac emerged. In 1999, Addison Labs sent Nasal Vac to the USDA National Animal Disease Veterinary Laboratory in Ames, Iowa. The report which returned stated: AThe B. bronchiseptica we isolated is a ribotype 4, fairly typical of dog and cat isolates, but most pig isolates are a ribotype 3, which means we should be able to distinguish it from most challenge strains we would use. The vaccine strain was non-hemolytic and did not kill macrophages like most of the virulent strains we use. We also didn't see any reaction with a monoclonal to the adenylate cyclase, thus it appears that it is not producing a toxin. We saw some evidence that it is **producing some purported adhesins (FHA) and possibly others that it is not (pertactin?), and it appeared to attach fairly efficiently to cells in vitro. Therefore, you may have an interesting strain that is producing some of the adhesins but not the toxins (such as adenylate cyclase and DNT), thus its ability to colonize without causing disease.@**

15) What is the shelf-life of Nasal Vac?

Nasal Vac has a shelf-life of 21 months from date of bottling and potency testing. It must be stored in the refrigerator until used. International orders will have at least 15 months of shelf-life remaining before shipment is approved.

16) What field efficacy studies have been conducted?

During the early 1980s, a field trial involving two herds [Herd A: 120 head (PAR) and Herd B: 1200 head (NPAR)], where every other litter was vaccinated and reared side-by-side demonstrated: 1) no clinical signs from atrophic rhinitis in vaccinated offspring (Herd A & B), 2) shorter interval to market (Herd B), or 3) greater average market weight in vaccinates (Herd A). Nasal Vac shaved-off 10 days to market and reduced lung scores to near zero. During 1998, field trials in Mexico demonstrated the value of Nasal Vac. One of the herdsmen with a progressive AR herd was

to run a study with controls to provide evidence for adoption of the product. Early on he found Nasal Vac worked so well, that he dropped the study and vaccinated even the controls in the next series of litters and saved over $3,000.00 (U.S.) worth of antibiotics. Gortie International coordinated these Mexican studies.

17) Will Nasal Vac protect against neonatal bordetellosis?

Absolutely yes.

18) Will Nasal Vac protect against Strep. suis?

Good scientific and anecdotal evidence suggests this is the case. Many DVMs only use Nasal Vac for targeting their Strep. suis herds.

Neonatal Bordetellosis can result in subtle early upper respiratory pathology (loss of cilia or ciliostasis) predisposing the system to more significant pulmonary damage from *Pasteurella multocida* (Pm, Types A&D) and *Streptococcus suis* (Ss). The action of Bb dermonecrotic toxin (DNT) on nasal mucosa is a precondition of the growth of Pm in the nasal cavity (Elias et al., 1992). **Pigs preinoculated with Bb were predisposed to Ss infection (Vecht et al., 1989). *Bordetella bronchiseptica* injury (damage of ciliated respiratory epithelium) in neonates can impact function of mechanical pulmonary clearance or sweeping away of unhealthy materials (microbes, dust particles, cellular debris).** This natural physical mechanism is extremely important for mucous trapping and sweeping away dust, bacteria, viruses, and other microbes from the pulmonary system. A compromised lung and pulmonary system can progress to more serious altered function and inflammation, such as pneumonia. This usually results in increased morbidity (unthrifty growers), poor performance on finishing floors (lowered ADG), mortality, increased medication and labor costs, and condemnations at slaughter. Anecdotal reports from swine practitioners suggest that Nasal Vac does afford protection against S. suis in swine herds. Many DVMs use Nasal Vac just for this purpose.

19) Will Nasal Vac protect against other PRDC pathogens, such as Haemophilus parasuis, Mycoplasma and Pasteurella multocida Type D?

Dr. SL Brockmeier reported in 2004 (Vet Micro) that prior infection by Bb increases nasal colonization by HPS. This suggests that a non pathogenic early colonizer, such as Nasal Vac, could also protect to a degree against pathogenic HPS. Although, no research data supports the contention that Nasal Vac protects against Mycoplasma, intuitively it makes plausible sense that it might if the physical pulmonary clearance mechanism can be protected. Nasal Vac definitely affords protection against colonization by Pasteurella by protecting ciliated epithelium. Pasteurella require prior insults to the epithelium before they can attach and cause damage by releasing toxins which enter the submucosa and go systemic. Pathogenic Bordetella predispose the epithelium for Pasteurella damage. Nasal Vac protects against invasion and colonization by pathogenic Bordetella.

20) When is Nasal Vac administered and what route is recommended?

Days 1-3 of life, intranasally **simultaneous with routine baby pig processing.**

21) What is the mechanism of protection afforded by Nasal Vac?

Competitive exclusion is a new generation approach to disease prevention and control. Nasal Vac works primarily by this mechanism of preemptive-colonization during the critical first 3 weeks of life. Immunity may play a role after 21 days. This new technology offers the veterinarian and production manager a new unique tool in the fight to control respiratory disease in intensive swine units. Use can decrease labor costs, decrease antibiotic usage, decrease production times and increase profits.

22) Will maternal interference cause problems with use of Nasal Vac in piglets?

No evidence of maternal interference has been uncovered from our research or over many years of field use of this product. Sows naturally infected with Bb or immunized with commercial or autogenous bacterins containing killed Bb will provide piglets' colostrum containing specific IgG antibodies to Bb. This passive immunity will provide systemic protection against deep turbinate damage from Bb toxins but these **IgG antibodies will not protect the respiratory epithelium surface from infection and colonization by pathogenic Bb**, nor will they interfere with our vaccine activity. Predominantly IgA secretory antibody protects the upper airway ciliated mucous layer. Secretory antibodies (mucosal immunity) are generally produced by localized infections of the epithelial surfaces (respiratory or intestinal mucosa) and are not generated in response to systemic vaccination. Plasma cells in the lamina propria immediately below the basement membrane of the surface epithelia produce IgA secretory antibodies. Slight amounts of IgM have been detected in respiratory mucus. IgG also provides protection for the deeper airways (bronchioles and alveoli). IgM and IgG classes of immunoglobulins in the deeper respiratory system may be the result of active immunization. Immunoglobulins (IgA, IgG, IgM) are present in colostrum to provide passive protection for the newborn.

23) What are the advantages of Nasal Vac?

Nasal Vac is a unique tool offering a means for potentially reducing therapeutic antibiotic use. **Advantages of competitive exclusion of respiratory disease by Nasal Vac are listed below**.

- Only one dose is required.
- No needle shock or injection site abscess.
- No anaphylaxis.
- No endotoxin reactions or production set-backs.
- Labor Saving. Nasal Vac is administered while the baby pig is being processed so the pig is not handled or stressed unnecessarily.
- Baby pig processing friendly (no extra labor).
- Intra-nasal route; no injection site reactions or lesions.
- No maternal interference.
- New generation technology (mucosal ciliary receptor saturation).

- Increased weaning weights.
- Reduces days to market.
- Improved market weight for given feeding interval.
- Reduction in respiratory disease treatments (savings in drugs, labor, stress on animals).
- Pneumonia/pulmonary infections reduced during grower/finisher periods.
- Lung pathology, condemnations, and peelouts reduced.
- Reduced death loss.
- Proven Safety Record.
- No known zoonotic or human health concerns.
- USDA Licensed Production Facility.

24) What kind of return can be expected?

Expected return per finish pig is $10.00 each in superior weight gain (performance), reduced labor and antibiotic demand. Finish pigs, vaccinated with Nasal Vac, reached finish weight (225 lbs) 10 days earlier than non-vaccinates. The price of hogs will impact this estimate to a large degree.

25) Can Nasal Vac be administered concurrently with other vaccines and intranasal products?

Although no incompatibilities have surfaced, this could potentially be a problem if both products are applied concurrently. Spacing of 2 - 3 days reduces this concern. Certain modified live intranasal vaccines have been used concurrently without loss of efficacy. Controlled research data on concurrent administration will not normally be available. Each situation should be evaluated and efficacy monitored by the attending veterinarian. Our technical services veterinarian is available to thoroughly investigate each concern prior to giving the go ahead.

26) How safe is Nasal Vac?

Very safe. Nasal Vac is avirulant and USDA licensed. One concern of all live vaccines is the potential for reversion to virulence. Backpassage safety studies were required by APHIS prior to licensing to prove that reversion was unlikely. Another aspect is that this Bb strain was not toxigenic initially. Each serial is safety tested in animal models. This product is in use by numerous practitioners across the U.S. and internationally. No safety complaints have arisen. Addison Labs supports the medical principle of "First do no harm."

27) How do I order and how will it be shipped?

Licensed DVMs can place orders by calling Addison Labs directly at 1-800-331-2530. Ethical veterinary distributors also carry Nasal Vac. Nasal Vac product can be drop-shipped to farms under a veterinarian's order. Product is normally shipped on wet ice by ground UPS depending on destination, Monday-Thursday. Extreme temperatures may require next day air UPS. FEDEX may occasionally be used. Nominal shipping charges are normally paid by the veterinary clinic. International orders are directed to Karlin Yaeger, Global Sales Manager (kyaeger@addisonlabs.com). International shipments normally require a forecast and a 90 day lead time. Small international orders can be accommodated on a personalized basis unless distributors have exclusivity in your country. Nasal Vac is

currently registered in USA, Mexico, Philippines, and South Korea. Other countries are pending.

Conclusion:

This new technology (mucosal ciliary receptor saturation) offers the veterinarian and production manager a new unique tool in the fight to control respiratory disease in intensive swine units, decrease labor costs, decrease antibiotic usage, decrease production times, and increase profits.

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