Active Feeding strategy to modulate immune response and improving productivity in PRRSv positive wea, DVM, ned piglets

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Executive Summary

Porcine Reproductive and Respiratory Syndrome (PRRS) represents one of the biggest global threats to the swine industry, not only due to its direct effects on the reproductive and respiratory systems, but also because of its profound impact on the animal's systemic and metabolic health. The "Active Feeding" strategy proposed in this report represents a paradigm shift, moving from conventional nutritional support to a targeted intervention that addresses the central pathophysiological causes of Porcine Reproductive and Respiratory Syndrome Virus (PRRSv) infection.

This strategy is based on the principle of the "gut-lung axis," which recognizes the interconnectedness between the intestinal microbiota and the respiratory immune response. By selectively modulating the gut microbiome and providing specific immunonutritional support, it is possible to counteract virus-induced inflammation, optimize nutrient utilization, and enhance the host's inherent resilience.

Key recommendations include the incorporation of specific probiotics and prebiotics, such as Mannan Oligosaccharides (MOS), to promote the proliferation of beneficial bacterial genera like *Prevotellaceae-NK3B31-group* and *Prevotella*, while suppressing pathogens such as *Campylobacter* and *Desulfovibrio*. Additionally, the inclusion of functional ingredients that mitigate systemic inflammation and promote rapid growth is proposed.

It is anticipated that the implementation of this strategy will result in a reduction of clinical symptoms (e.g., lower fever, less diarrhea), an improvement in productive parameters (such as average daily gain and feed efficiency), and a general strengthening of the animal's immune system, which translates into greater profitability and sustainability in swine production.

1. The PRRSv challenge: Beyond a respiratory disease

1.1 The economic and health impact of PRRSv

The PRRS virus is a single-stranded, positive-sense RNA pathogen belonging to the *Arteriviridae* family.[1] This virus represents a significant challenge for the global swine industry, primarily due to its ability to cause reproductive disorders in sows and a debilitating respiratory disease in piglets. Clinical symptoms in piglets include fever, tachypnea, dyspnea, diarrhea, and slowed growth. These clinical manifestations are exacerbated by secondary bacterial infections, which increase morbidity and mortality.

Infection with PRRSv induces a complex and often ineffective immune response that, in turn, creates a substantial physiological burden on the animal. This systemic immune response is costly in terms of energy and nutrients. The organism diverts valuable metabolic resources, which would normally be dedicated to growth and tissue synthesis, to activate the non-specific immune response and fight the virus.[2] This diversion of energy and nutrients largely explains the reduced feed intake and growth suppression observed in infected piglets.[3] Therefore, the impact of PRRSv should not be considered as a localized problem in the respiratory tract, but as a systemic and multifaceted disease that imposes a serious energy and metabolic cost, directly affecting productivity.

1.2 Host resistance

Host resistance to PRRSv is influenced by a combination of genetic and environmental factors. While significant genetic differences between breeds have been demonstrated, resistance is also critically affected by the animal's environment.[1] A crucial component of this environment is the endogenous microenvironment formed by the gut microbiota.[1] Resistance is not a simple matter of evading infection, but of how the animal responds to it.

The optimal response is defined by a low viral load and high weight gain, even after infection.[1] This approach is in contrast to susceptible animals, which show a high viral load and low or no weight gain.[1, 1] This concept of resistance to viral challenge, where the animal maintains its productive performance despite infection, is the fundamental objective of a proactive feeding strategy. The evidence that microbiota influences the host's response establishes the basis for a nutritional intervention that not only mitigates symptoms but also strengthens the piglet's inherent ability to resist and recover from infection.

2. The gut-lung axis: PRRSv pathophysiology in the intestine

2.1 Virus-induced dysbiosis

The gut-lung axis is an interaction system mediated by the gut microbiota.[1] Research has demonstrated a close link between the composition of the gut microbiota and respiratory infections, indicating that gut microbes can influence lung health.[1] PRRSv infection causes a dramatic alteration in the gut microbial community, breaking the state of balance and stability that characterizes a healthy microbiota.[1]

Studies indicate an increase in the abundance and diversity of the gut microbiota after PRRSv infection, a finding that suggests a breakdown of the microbial ecosystem's homeostatic state.[1] For example, a high-virulence PRRSv strain has been observed to induce earlier and more aggressive dysbiosis, which includes a reduction in microbial diversity and the loss of beneficial commensal anaerobic bacteria, such as *Roseburia*, *Anaerostipes*, *Butyricicoccus*, and *Prevotella*.[1] This alteration in the microbiome correlates with a greater severity of clinical symptoms and viremia.[1] The findings demonstrate a bidirectional physiological interaction where lung inflammation and systemic stress contribute to gut dysbiosis, and this dysbiosis, in turn, can exacerbate the overall clinical picture.

2.2 The correlation between gut composition and disease severity

One of the most significant conclusions from the research is that the composition of the gut microbiome is a determining factor for the clinical outcome of the disease. Piglets that showed the best clinical outcomes after co-infection with PRRSv and circovirus type 2 (PCV2) had a greater microbial diversity in the fecal microbiome.[1] Conversely, pigs with the worst outcomes had lower microbial diversity, which indicates that microbiome diversity can be a protective factor and an indicator of resilience.[1]

The inflammatory and metabolic stress state induced by the infection disrupts the microbiome's balance, which creates a gut environment that is less favorable for commensal anaerobic bacteria and more prone to the proliferation of opportunistic pathogens. This alteration is clearly seen in the correlation between the abundance of certain bacteria and the severity of the disease. The reduction of desirable anaerobic bacteria, such as those from the genus *Prevotella*, has been directly correlated with the severity of the infection, suggesting a clear causality where a weakened microbiome contributes to more severe disease.[1] This negative cycle (disease causing dysbiosis, and dysbiosis worsening the disease) underpins the need for a nutritional intervention that breaks this pattern.

3. The microbiota as a predictor and modulator of PRRSv resistance

3.1 Identification of key microbiota

Analysis of the gut microbiome has identified specific bacterial genera that correlate positively or negatively with the pig's response to PRRSv infection. These findings provide a scientific basis for designing an "Active Feeding" strategy that actively promotes the proliferation of beneficial bacteria and the suppression of harmful ones.

The findings indicate that the abundance and diversity of beneficial bacteria, such as *Prevotellaceae-NK3B31-group*, are associated with a lower viral load and higher weight gain in resistant pigs.[1] Other beneficial genera identified include *Prevotella*, *Faecalibacterium* and the family *Ruminococcaceae*, whose abundance was negatively correlated with disease severity.[1]

Conversely, pathogenic or opportunistic genera were identified that are associated with poorer clinical outcomes. *Campylobacter* and *Desulfovibrio* were found in higher abundance in susceptible pigs.[1] These genera have been associated with diarrhea and immune system imbalance.[1] Infection with a virulent PRRSv strain was also correlated with a higher abundance of *Treponema* and *Methanobrevibacter*.[1]

The following table summarizes the "Microbiome Blueprint for Active Feeding," providing a guide for diet formulation:

Table 1: The microbiome blueprint for Active Feeding

Bacterial Genus	Association with PRRSv Response	Implication for Active Diet
Prevotellaceae-NK3B31-group	Positively correlated with weight gain and negatively with viral load.[1]	**Goal:** Promote its abundance.
Prevotella	Negatively correlated with disease severity.[1]	**Goal:** Promote its abundance.
Ruminococcaceae	Higher abundance in resistant pigs; promotes intestinal barrier function.[1]	**Goal:** Promote its abundance.
Faecalibacterium	Negatively correlated with disease severity.[1]	**Goal:** Promote its abundance.
Campylobacter	High abundance in susceptible pigs; associated with diarrhea.[1]	**Goal:** Suppress its abundance.
Desulfovibrio	High abundance in susceptible pigs; associated with immune imbalance.[1]	**Goal:** Suppress its abundance.
Christensenellaceae-R7-group	High abundance in susceptible pigs; negatively correlated with weight gain.[1]	**Goal:** Suppress its abundance.

Parabacteroides	Positively correlated with viral load and negatively with weight gain.[1]	**Goal:** Suppress its abundance.
Treponema	Higher abundance in pigs infected with a virulent strain.[1]	**Goal:** Suppress its abundance.
Methanobrevibacter	Higher abundance in infected pigs; associated with low growth rate.[1]	**Goal:** Suppress its abundance.

3.2 The predictive nature of the microbiome

A fundamental discovery is that differences in microbiome composition already existed before PRRSv infection in pigs that later showed resistance or susceptibility phenotypes.[1] This observation transforms the perspective on nutrition: instead of being a reactive therapy for sick animals, "Active Feeding" becomes a proactive strategy to build a state of metabolic and microbiological resilience from the start.

The evidence suggests that the goal is not simply to cure the animal, but to strengthen its capacity to resist the most severe effects of the virus before an infection occurs. By fostering a "resilience" microbiome with the right bacteria, the animal is equipped to more effectively manage the viral load and inflammatory response, allowing it to maintain productive performance even under challenging conditions. This strategy shifts the focus of farm disease management to the prevention of its most severe manifestations, addressing animal health from a long-term welfare perspective.

4. Immuno-nutritional components for a PRRSv-targeted diet

4.1 The role of probiotics and prebiotics

Probiotics and prebiotics are key components of the Active Feeding strategy, as they act directly on the gut microbiome to modulate the host response. Probiotics, such as *Bacillus subtilis* and *Lactobacillus acidophilus*, work through competitive exclusion of pathogens, production of antimicrobial compounds, and improvement of nutrient digestibility.[4] However, their most significant function in the context of PRRSv is their ability to act as immunomodulators, improving macrophage activity and increasing local antibody levels.[4]

Prebiotics, on the other hand, are non-digestible ingredients that serve as a substrate for the selective proliferation of beneficial microorganisms in the gastrointestinal tract.[4] This fosters a healthy microbiota which, in turn, improves host health.

4.2 The anti-inflammatory and immunomodulatory core

The systemic immune response to PRRSv, although necessary, is the main source of pathological symptoms, including fever and inflammation. The goal of an Active Feeding diet is to mitigate these negative effects. Research on Mannan Oligosaccharides (MOS) provides a perfect case study for this approach.[1] Piglets fed MOS and exposed to PRRSv showed a reduction in fever and an improvement in gain-to-feed (G:F).[1]

Analysis of immune mediators revealed why: pigs with MOS had a lower concentration of the pro-inflammatory mediator TNF-α and a higher concentration of the anti-inflammatory mediator IL-10.[1] This evidence demonstrates that the diet can reduce the "inflammatory tax" that the disease imposes on the pig's metabolism, allowing energy to be redirected towards growth and recovery. The ingredient matrix for an Active Feeding diet must include components that act in this way. In addition to MOS, functional proteins like spray-dried plasma can also improve gut barrier function and modulate the immune response, reinforcing the central principles of this strategy.[2] By limiting systemic inflammation, nutritional efficiency is maximized and productivity is improved even in sick animals.

The following table summarizes the key findings from the MOS study, which represents the primary evidence for the effectiveness of key components in an Active Feeding diet.

Table 2: MOS: Evidence of immuno-nutritional efficacy[12]

Parameter	Findings in PRRSv-Infected Pigs Fed MOS	Functional Implication
Feed:Gain (F:G)	Improved during days 7 to 14 post-infection (P=0.041).	Improves d Feed efficiency and productive performance.
Rectal Temperature (RT)	Decreased on days 7 and 10 post-infection (P<0.01) compared to control group pigs.	Reduces fever, which decreases metabolic energy expenditure.
TNF-α	Reduced serum concentrations on day 14 post-infection (P=0.028).	Decreases the pro-inflammatory response.
IL-10	Increased serum concentrations on day 14 post-infection (P=0.036).	Increases the anti-inflammatory response, promoting immune balance.

White Blood Cells (WBC)	Increased on days 3 and 7 post-infection.	Strengthens the immune system in the early phase of infection.
Lymphocytes	Increased on day 7 post-infection.	Supports the cellular immune response.

5. Proposed formulation guidelines for the "Active Feeding" diet

5.1 A phased nutritional approach

The Active Feeding strategy should be implemented in a phased approach to maximize its effectiveness.

1. **Phase I (Proactive):** This diet should be administered to all piglets from weaning, regardless of their health status. The goal is to build a robust and resilient microbiome before potential virus exposure. The focus is on prebiotics and a multispecies probiotic blend that promotes the identified beneficial genera. Also Functional Proteins as plasma derived products and Egg derived products are essential to decrease inflammation and help the gut structure.

2. **Phase II (Reactive):** For piglets confirmed or suspected to be PRRSv-positive, the diet should be adjusted to include a higher concentration of key components. This phase aims to counteract the disease's impact with an increase in high-energy density nutrients and immunomodulators to support recovery.

5.2 Recommended ingredient profile

The Active Feeding diet should be formulated with ingredients that not only provide basic nutrients but also exert a specific physiological effect.

- **Functional Proteins:** Highly digestible protein sources should be prioritized to reduce the load on the gut and provide the amino acids necessary for the immune response and growth. The inclusion of proteins like spray-dried plasma and egg derived compounds are valuable, as it has been shown to improve gut barrier function and modulate the immune response.[2]
- **Prebiotics:** Mannan Oligosaccharides (MOS) should be a central component due to their proven ability to reduce inflammation and improve feed efficiency in PRRSv-infected piglets.[1] The inclusion of other fermentable fibers to stimulate colonic fermentation should be considered.[6]
- **Probiotics:** A multispecies probiotic blend is recommended, including strains of *Lactobacillus* and *Bifidobacterium*, which are known for their ability to strengthen immunity and suppress pathogen growth.[4] The goal should be a formulation that encourages the abundance of the beneficial genera identified in this report.

- **Fatty Acids:** It is advisable to include high-quality fats, such as Omega-3 polyunsaturated fatty acids.[7] These fatty acids have been shown to have an anti-inflammatory effect in humans and are a dense, low-inflammation energy source.[9]

- **Vitamins and Minerals:** The formulation must ensure optimal levels of vitamins and minerals, as they are essential cofactors in immune function and metabolic processes.

6. Conclusion

The "Active Feeding" strategy for PRRSv-positive weaned piglets is a scientifically grounded approach that addresses PRRSv infection not just as a respiratory disease, but as a systemic condition influenced by the gut-lung axis. The evidence demonstrates that the composition of the gut microbiome is a determining factor in the disease outcome, and that the most resistant piglets have a particular microbiota profile even before virus exposure.

By incorporating components such as MOS and probiotic blends that reduce the inflammatory burden and improve metabolic efficiency, the diet is not limited to treating symptoms but empowers the animal's capacity to mitigate the most devastating effects of the infection. This proactive strategy, by fostering a resilience microbiome from weaning, has the potential to significantly improve the health and well-being of pigs, which translates into superior productive performance and greater long-term sustainability in the swine industry.

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