Reducing antimicrobial usage starts with correct management of the gut

Productivity in animal production has been advanced through innovation for many years. One of these innovations was the use of antibiotics for disease treatment, prevention and growth promotion. They have been the most effective means of maintaining or improving the health and feed efficiency of animals raised in conventional rearing systems, but their use has come at a cost.

by Dr Maria Walsh, Global Swine Marketing Director, DSM Animal Nutrition & Health. www.dsm.com

There is now overwhelming evidence to link the misuse and over-use of antibiotics in animal production and human medicine and the spread of antimicrobial resistance (AMR) in the wider population. Antibiotic usage rates are highest in the swine production industry, followed by poultry and ruminants.

Currently, AMR is one of the world's leading health threats, claiming 700,000 lives a year. It will become the single leading cause of death by 2050 if not tackled.

At DSM Animal Nutrition & Health, we believe in sustainable food systems and that the livestock industry can transform itself from within to be part of the solution to the world's sustainability challenge.

We support the responsible use of antibiotics to ensure animal health and welfare through the deployment of alternative nutritional solutions and innovations.

The swine industry in many parts of the world is continuing to evolve their production practices in response to this growing societal threat.

In more recent years, legislation banning the use of antimicrobials as growth promoters in large swine markets such as China and the upcoming 2022 ban of therapeutic ZnO use in feed in Europe are accelerating this change, along with commitments such as those outlined by the European Green Deal to halve the usage of antibiotics in animal production by 2030. These changes have led to a fundamental change in thinking about gut health and its relationship with animal performance.

It is generally widely accepted that there is no single alternative solution that can replace the tools of the past and deliver the same consistent response that is associated with antibiotics.

However, what the industry has learned is that a multifaceted approach is necessary that takes into consideration the complexities of the interactions between the animal, its gut microbiome and its feed.

In swine production, weaning is the most critical event that has the potential to make or break production success.

Supporting pigs successfully through this extremely stressful time will pay dividends in the long run.

Prepare for success

Navigating the perils of weaning successfully starts with preparing for that piglet while still in-utero.

There are two main areas that are considered vital to successful preparation:

- Early microbiome development.
- Robust immune development.

It is now recognised that the gastrointestinal microbiota plays an essential role in maintaining the health status of humans and animals.

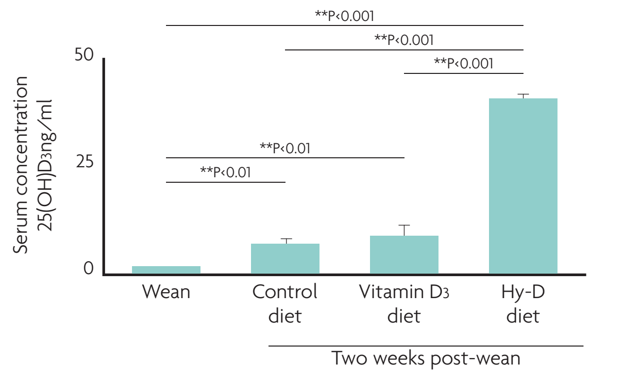
The development of the gut microbiome of piglets begins as soon as they leave the sterile conditions of the uterus and are largely influenced by the microbiome of the sow and her immediate environment. Developing and maintaining a stable and diverse gut microbiome is critical to pathogen resilience and optimum functioning of the gut in an environment of reduced antibiotics.

There are numerous nutritional tools available to support the development of a balanced bacterial community in the gut.

The administration of probiotics, such as Enterococcus faecium, appear to be most successful when administered to both the sow during lactation to direct early engraftment of benefit strains in the developing but still malleable gut microbiome and sustained through continuous administration during the post-weaning period.

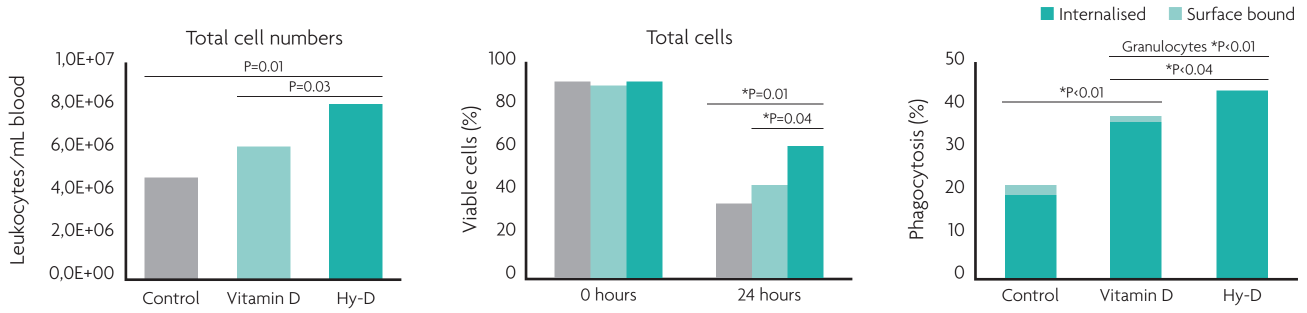
Another key consideration in the early preparation for healthy, high

Continued on page 9



Newly weaned pigs. Treatments:
Control: 1,500 IU/kg Vitamin D_3
Vitamin D_3: 3,500 IU/kg Vitamin D_3
Hy-D: Rovimix Hy-D (50µg 250HD3/kg of diet) + 1,500 IU/kg Vitamin D_3 for 14 days

Fig. 1. Supplementation of vitamin D_3, and the 25-OH vitamin D_3 form in particular, increases immune cell number and activation in weanling pigs (Konowalchuk et al., 2013).



Continued from page 7
vitality piglets is a robust immune system. Newly born piglets are entirely dependent on passive immunity from sows' colostrum to protect them in early life until their own immune system is fully developed. Micronutrients including some vitamins (D_3, E, C and B) and minerals are known to have immunomodulatory benefits.

At birth, the vitamin status of piglets is highly dependent on the levels of vitamin supplement to the sows' feed. Vitamins E and C have long since been recognised for their ability to act as potent antioxidants that prevent oxidative damage of immune cells. The pig's requirement for vitamin E is elevated during immune development and activation.

At birth, the vitamin E level of piglet blood is highly dependent on the vitamin E status of the sow. Piglet viability can be enhanced through optimum vitamin E supplement of sows through gestation and into lactation.

More recently, the role of vitamin D_3 or more importantly its main metabolite, 25-hydroxy (OH) vitamin D_3 in immunomodulation is just starting to be understood.

One of vitamin D_3's primary roles is not only to support the activation of immune cells and production of antimicrobial peptides but also to limit excess responses. Pigs are born with very low levels of blood 25-OH vitamin D_3 which seldom reach the minimum, much less the optimum, range to support immunity.

Now understanding the critical role of vitamin D_3 to immune function, weaned pigs can be at a disadvantage without adequate supplementation during a very stressful period in the production cycle. Konowalchuk et al., 2013 reported that supplementation of vitamin D_3, and the 25-OH vitamin D_3 form in particular, increased immune cell number and activation in weanling pigs (see Fig. 1).

Protect the gut barrier

It has been proposed that a main mode of action of antibiotic growth promoters is the promotion of an anti-inflammatory gut environment.

Inflammation can be classified as:

- **Physiologic:** the balance between tolerance to the resident microbiome and food antigens and reactivity to pathogens.
- **Pathologic:** an acute response to toxins and infection.
- **Metabolic:** a low-grade inflammation produced by metabolic surplus of nutrients.
- **Sterile:** a non-pathogenic inflammation in response to chemical (oxidative stress), physical (microbiota-derived components) or metabolic (non-starch polysaccharides from dietary components) stimuli.

Striking the right balance between reactivity of the immune system in the gut, and avoidance of unnecessary responses is the ultimate goal, although knowledge in the area is still developing. However, there are known feed additives that act as immune-stimulants or direct anti-inflammatory compounds, target feed antigens and microbe-specific molecular patterns (MAMPS); all of which can be used as part of a programme to boost health in specific management conditions.

An example of an inducer of physiological inflammation is peptidoglycan (PGN). Peptidoglycan is the major polymeric component of Gram-positive bacterial cell walls, and a thin layer is also present in Gram-negative bacteria.

Peptidoglycans fragments are continuously being released into the intestine as part of the normal bacterial cell turnover process.

However, damage to the gut epithelium is inevitable (for example mycotoxins, bacterial toxins) and allows PGNs to reach and activate receptors on the basolateral surface of epithelial cells, such as TLR2, activating an inflammatory pathway.

A novel muramidase feed enzyme (Balancius) has recently been authorised for use in weanling pigs that cleaves the 1,4-beta-linkages between N-acetylmuramic acid and N-acetyl-D-glucosamine residues in peptidoglycan. This decreases the potential inflammatory signal PGN causes. The breakdown of PGN can also result in muramyldipeptide (MDP) formation, which in turn is sensed by intracellular receptors (such as NOD2) and has an anti-inflammatory effect.

Table 1. Inducers of inflammation and potential solutions.

Type of inflammation	Inducer examples	Potential solution
Physiological	LPS, peptidoglycans, bacterial flagellin	Muramidase
Pathologic	E. coli, streptococcus, salmonella, mycotoxins	Essential oils, organic acids, probiotics
Metabolic	Oxidative stress	Vitamins
Sterile	Allergenic proteins, biogenic amines, beta-mannans, NSPs	Enzymes

Organic acids administered through feed have a long history of use in weanling pig diets and have emerged as the cornerstone of weanling pig gut health programmes in many markets wishing to reduce reliance on antibiotics and ZnO. One of the primary roles of these acids is to create a gut environment that is less favourable to Gram negative bacterial pathogens, thus reducing pathologic inflammation.

There are a wide variety of acids available for use in swine, with each having a range of different properties and characteristics. But not all acids are created equal. Common forms include salt of an organic acid or a blend of organic acids (for example, butyric, citric, fumaric, propionic, etc). Diets can sometimes include an inorganic acid (for example, phosphoric).

Two aspects which are considered the most important determinants of acid effectiveness in swine nutrition are water solubility and dissociation constant (pKa). An ultra-pure form of benzoic acids (VevoVitall) has been shown to be very effective in supporting benefical intestinal bacterial communities, enhancing nutrient digestibility and in turn improving pig growth performance.

Ultra-pure benzoic acid is water insoluble preventing dilution of its effect in the digestive tract and has a relatively high pKa value making it a very effective feed preservative with antimicrobial activity along the length of the gut.

Improve resilience

Oxidative stress is a related but independent issue relative to inflammation, which is often overlooked. It is an imbalance between the oxidants and antioxidants in favour of the oxidants, leading to a disruption of redox signalling and molecular damage in tissues.

Basically, reactive oxygen species (ROS) are produced in the intestine in response to stimuli such as chronic infection, inflammation, and heat stress, which results in damage of the intestine, bacterial translocation, and additional inflammation of the intestine.

Moreover, the production and systemic transport of oxidised lipids and proteins from the intestine contributes to oxidative stress in other tissues, such as liver and muscles. The maintenance of redox balance represents a cornerstone for effective immunity and health and oxidative stress has been linked to optimum gastrointestinal functionality. Pig management and nutritional tools are the centre of strategies to maintain optimal redox balance in pigs.

The effects of vitamin C, E, and A and Se to decrease the negative

impact of systemic oxidative stress, induced by health stress for instance, have been widely reported. The required levels of supplementation of those vitamins in conditions of heat stress are generally above the minimum requirements in feed.

For example, supplementation of 200 IU/kg vitamin E combined with 1ppm Se mitigated the impact of heat stress on intestinal barrier integrity and glutathione peroxidase activity in pigs.

Kim et al. (2016) also found that the acute phase protein response to an ETEC challenge was reduced by supplementation with vitamin E at 200 IU/kg. This response was thought to be due to reduced cellular oxidative cell damage as a result of vitamin E supplementation.

Other additives such as polyphenols, which have a local intestinal antioxidative mode of action, have been proposed and could be one of the tools to reduce oxidative stress in pigs, however they are much less bioavailable than vitamins and in most cases are not a good substitute for vitamin E.

Nutritional strategies to boost health of the piglet's gut post-weaning should:

- Start with the sow to prepare the piglet for optimum gut microbiome and immune development.
- Protect the gut barrier by reducing inflammation due to external stimuli.
- Modulate inflammation arising from oxidative stress.

Such strategies are mainly based on the direct supplementation of essential nutrients when pigs are in key stages of development or under high levels of challenge, the supplementation of complementary enzymes to modify the nutrient digestion kinetics or target deleterious substrates in feed, the supplementation of additives with direct immune modulatory or antioxidant function, and additives maintaining microbial balance.

However, the knowledge of the functionality of some of those feed additives is still limited. The development of feed additives targeting specific modes of action in the intestine will allow producers greater accuracy in the selection of additives and the design of nutritional programmes to boost health. ■

References are available from the author on request