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Executive summary

Antimicrobial resistance is a global and increasing threat. Stewardship campaigns have been established, and policies implemented, to safeguard the appropriate use of antimicrobials in humans, animals and plants. Restrictions on the use of antimicrobials in animal production are on the agenda worldwide. Producers are investing in measures, involving biosecurity, genetics, health care, farm management, animal welfare and nutrition, to prevent diseases and minimize the use of antimicrobials. Young animals (piglets, broiler chickens and calves) are particularly susceptible to diseases and disorders, and the use of antimicrobials on these animals is therefore relatively high. Functional nutrition to promote animal health is one of the tools available to decrease the need for antimicrobials in animal production. Nutrition affects the critical functions required for host defence and disease resistance. Animal nutrition strategies should therefore aim to support these host defence systems and reduce the risk of the presence in feed and water of potentially harmful substances, such as mycotoxins, anti-nutritional factors and pathogenic bacteria and other microbes. General dietary measures to promote gastrointestinal tract (GIT) health include, for example, the functional use of dietary fibres to stimulate gastrointestinal secretions and motility, lowering the protein content to avoid excessive fermentation of protein in the hindgut, and selective use of a combination of feed additives and feed ingredients to stabilize the intestinal microbiota and support mucosal barrier function. In addition, the use of organic acids may contribute to feed and water safety. This knowledge, used to establish best practices in animal nutrition, could allow the adoption of strategies to reduce the need for antimicrobials and contain antimicrobial resistance.

Key words: antimicrobial resistance, antimicrobial use, antimicrobials, antibiotic, gut health, animal production, animal health, feed, feed additives, animal nutrition

Introduction

Antimicrobial resistance (AMR) is an increasing threat to both human and animal health, and has reached concerning levels in many parts of the world. The inappropriate use of antimicrobials in human health care and animal production is believed to be a major driver of AMR. The World Health Organization (WHO) has published Guidelines on Use of Medically Important Antimicrobials in Food-Producing Animals. These include antibiotics, which are defined as naturally occurring, semi-synthetic or synthetic substances with bacteriocidal (bactericidal) or bacteriostatic properties at concentrations attainable *in vivo*. Antibiotics used in human medicine are categorized as 'important', 'highly important' or 'critically important'. Amongst those classed as critically important to human medicine are antibiotics such as aminoglycosides, third- and fourth-generation cephalosporins, fluoroquinolones, glycopeptides, macrolides, certain broad-spectrum penicillins and colistin, all of which are also used with food-producing animals.

Antibiotics are used in animal production as growth promoters (AGPs) and to prevent and treat disease (Sneeringer *et al.*, 2015). Van Boeckel *et al.* (2015) estimated that in 2010, 63 151 tonnes of antibiotics were used in animal production across 228 countries. The authors predict that antibiotic consumption will rise by 67 percent by 2030, and nearly double in Brazil, Russia, India and China, if no additional restrictions on their use are adopted. The WHO thus recently recommended avoiding the use of medically important antibiotics for growth promotion or for prevention of infectious disease that have not yet been clinically diagnosed in food-producing animals, and limiting the use of appropriate antibiotics to the treatment of animals that have been clinically diagnosed with an infectious disease within an herd (WHO, 2017a). The European Commission already decided to ban all AGPs in animal production in 2006. Initially, this was not without consequences. The preventive and therapeutic use of antibiotics prescribed by veterinarians increased in the first years after the ban (Cogliani, Goossens and Greko, 2011). However, countries such as Denmark and the Netherlands responded quickly by implementing additional measures. This included adopting very strict policies for the use of antibiotics, including a ban on the use of medicated feed, and adopting best practices in animal husbandry, nutrition and health care. This multifactorial and multi-stakeholder approach has led to a significant reduction in antibiotic use (MARAN, 2018), whilst maintaining high productivity and animal welfare. It is encouraging to note that the decline in antibiotic use in the Netherlands coincided with a reduction in the prevalence of (multi-)resistant bacterial pathogens (MARAN, 2018). In a meta-analysis of 81 studies, Tang *et al.* (2017) recently confirmed that restricting the use of antibiotics on food-producing animals was associated with a reduction in AMR.

In the United States, the new Veterinary Feed Directive (VFD), implemented on January 1, 2017, restricts the use of all antimicrobial products deemed important to human health for livestock applications. Specifically, such products can no longer be used for growth promotion purposes, and can only be used in feed when a veterinarian, supported by diagnostic procedures, identifies a specific infectious disease and prepares a VFD. Some antibiotics which are not used in human medicine can still be used for growth promotion purposes. A recent report prepared by the U.S. Food and Drug Administration reported that the sale and distribution of medically important antimicrobials decreased by 33 percent from 2016 to 2017 and by 43 percent from 2015 to 2017 (FDA, 2018). A similar approach was adopted in Canada on December 1, 2018, though no information on its impact on antimicrobial use is yet available.

The restricted use of antimicrobials is on the agenda worldwide. Producers adopt best practices in biosecurity, health care, animal welfare, genetics, farm management, feed handling and animal nutrition to the extent feasible from a practical and economical perspective, as well as an animal welfare point of view. In general, such measures focus on reducing infection pressure in the environment and increasing the animals' disease resistance and resilience. Minimizing stress, both social and environmental, well-targeted tailor-made vaccination schemes and, last but not least, health-promoting diets will contribute to disease resistance. Animal nutrition is concerned not only with the provision of the proper amount of nutrients needed for various bodily functions, such as reproduction and growth, but also, given its influence on the functions critical to host defence and disease resistance, with maintaining animal health.

Objective and scope

Antimicrobials are widely used in terrestrial and aquatic animal production. However, given the extent of their use, the objective of this paper is to provide guidance for animal nutrition strategies and options that can contribute to a healthy gastrointestinal tract (GIT) in swine, poultry and ruminants, and that will support the defence system of the host during critical transitions, when the risk of health disorders is significantly higher. Improved GIT health can in turn decrease the need to use antibiotics. Birth and weaning are examples of critical periods in the lives of new-born mammals such as piglets and calves. Relocation to other units at a relatively young age and immature status is a second important stress event that presents a challenge to animal health. Hatching and the two to three weeks post-hatch is a high-risk period in broiler chickens, because the young bird still has to develop a large part of their immune defence repertoire. It is thus not surprising that antibiotic use for enteric problems is relatively high in young animals (Merle *et al.*, 2014; van Rennings, 2018). Sows and dairy cows face a higher risk of infectious diseases around the time of farrowing and calving, respectively. Parturition, and the immediate start of lactation thereafter, is a metabolic and physiological challenge with an impact on disease resistance that creates opportunities for pathogens. In addition to the risk of enteric problems, the profusion of changes during parturition may also result in uterine, urinary tract and mammary gland infections. Dietary intervention, via feed or drinking water, is a viable option for promoting gut or GIT health and preventing or reducing the need for antibiotics, especially during these critical transition periods. In this document, "gut health" or "GIT health" will mean the absence of gastrointestinal disease, the effective digestion and absorption of feed, and a normal and well-established microbiota (Bischoff, 2011).

The other main application of antibiotics is in the prevention and treatment of respiratory disorders. Biosecurity, vaccination and climate control are the more obvious routes to reducing the risk of respiratory infections. However, recent information suggests that there is an important interaction between the gut and lung in host defence (Samuelson, Welsh and Shellito, 2015). It now appears possible that improving host defence in the gut through nutrition may contribute to higher resistance to respiratory infections. Unfortunately, there is a paucity of scientific information and practical application on this topic, which makes it an interesting area to research further.

This publication focuses mainly on dietary strategies, aiming to reduce the risk of enteric health problems during critical transition periods where antibiotic use is relatively high. The principles of host defence mechanisms that can be influenced and supported by animal nutrition are discussed. The main tools available for diet formulation, and feed and drinking water management are described. Finally, this publication discusses in more detail the practical application of dietary tools during critical transition periods in the lives of swine, poultry and ruminants, with an emphasis on the species categories for which antibiotic use is highest (e.g. piglets, broilers and calves).

General principles of gastrointestinal digestion and defence

SYMBIOSIS AND HOST DEFENCE

The microbiota and host have been described as a ‘superorganism’. The microbiota plays a key role in immunity, digestion and metabolism, and may even affect behaviour (Aziz *et al.*, 2013; Takiishi, Fenero and Câmara, 2017; Wu and Wu, 2012). The host and the microbiome live in symbiosis and are in homeostasis in a healthy animal. Beneficial microbes dominate the intestinal microbiome and opportunistic pathogens are controlled effectively (Bowring, Jenkins and Collins, 2015; Eeckhaut *et al.*, 2011; Huyghebaert, Ducatelle and Immerseel, 2011). The microbiota is normally in balance with the host. Of the bacterial phyla, *Firmicutes*, which includes the genera *Lactobacillus*, *Streptococcus*, *Staphylococcus* and *Clostridium*, is by far the most common in the gastric and small intestinal microbiota. In addition to *Firmicutes*, a relatively high proportion of *Bacteroidetes* can be present in the colon, caecum and in the ruminant foregut. These phyla contain a wide range of fibre-fermenting bacteria that produce short-chain fatty acids (SCFAs). The abundance of *Proteobacteria* and *Actinobacteria* is low. *Escherichia coli* and *Salmonella* belong to the *Enterobacteriaceae* family, which is part of the *Proteobacteria* group. It is only in neonatal piglets and calves, and in the immediate post-hatch period for chickens, that a relatively high abundance of *Proteobacteria* can be found, but this rapidly decreases over the course of the first few days of life. When the animal is in symbiosis with its microbiota, a high diversity of bacterial species with a relatively high abundance of beneficial bacteria and low abundance of potentially pathogenic bacteria (pathobionts) can be found. Bacterial species associated with health benefits include *Ruminococcus* spp., *Feacalibacterium prausnitzii* and *Bifidobacterium* spp.

The GIT has an ingenious system to control and manage both harmful and beneficial microbiota, and is the largest interface between internal organs and the outside environment of bacteria, viruses and parasites. The best dietary method of supporting gastrointestinal health without the use of antibiotics is to follow strategies that support the host defence system. An important part of the defence against pathogens involves digestive and absorptive functions. The host permits commensal bacteria to interact, and to ferment and synthesize nutrients, but at the same time needs to maintain the microbiome within narrow ranges using GIT secretions, motility and mucosal barrier function. In particular, pH and the retention time of the digesta in the different sections of the GIT has to be strictly controlled in order to regulate the microbiome and optimize digestive functions. Disturbances or disorders of these digestive functions may cause an imbalance between the microbiome and the host, with detrimental effects on animal health.

Some of the key comparative differences in the anatomies of swine, poultry and ruminants are shown in Figure 1. Swine and poultry have a monogastric digestive system. The pH in the stomachs of *ad libitum*-fed swine ranges from 3.5 to 4.5, which is subsequently increased as a result of the secretion of bicarbonate in pancreatic juice to a pH of 5.5 to 6.5 in the small intestine. Finally, fermentation of the remaining material takes place in the large intestine, producing SCFAs. A large proportion of the secreted water and electrolytes is re-absorbed for re-use. The pH in the caecum and colon of swine also normally ranges from 5.5 to 6.5.

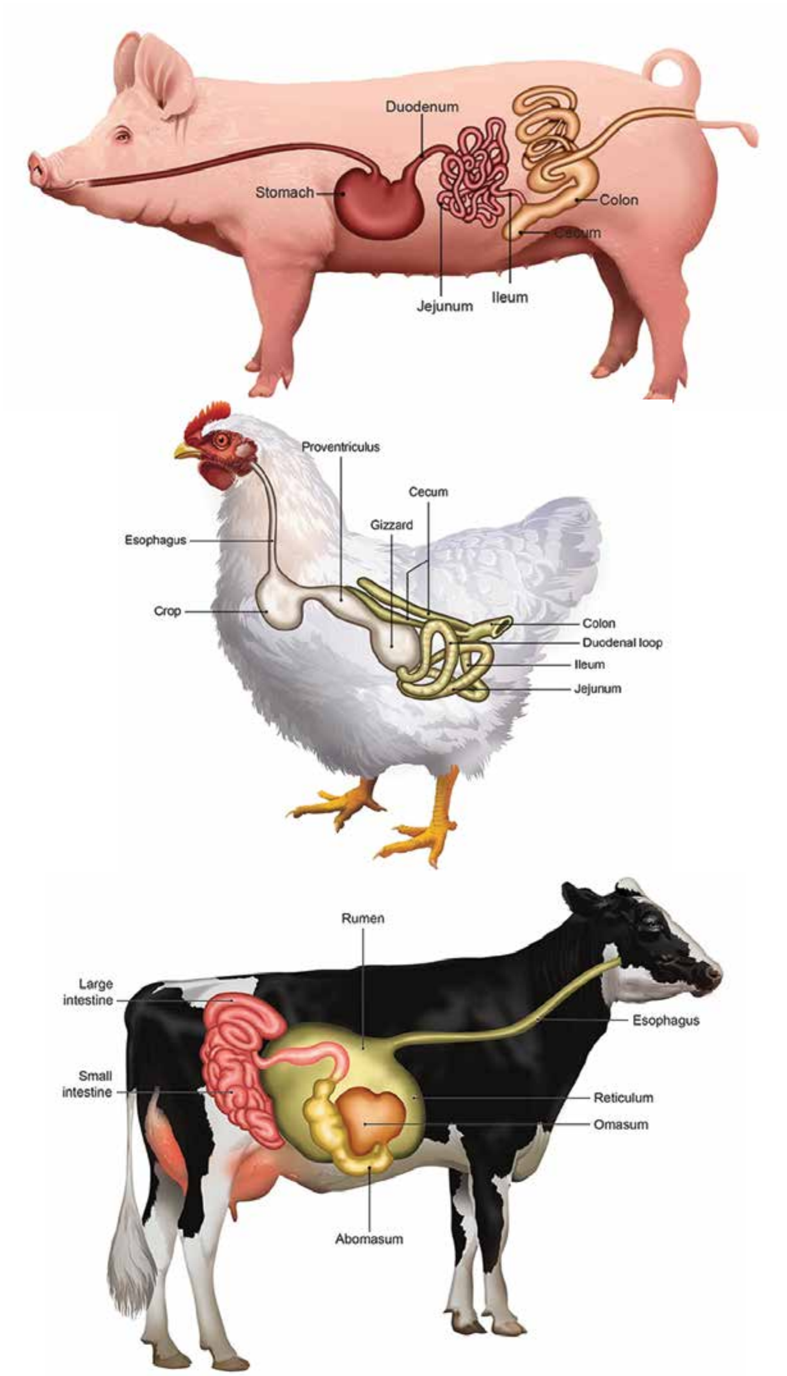
In poultry, the proventriculus and gizzard have functions similar to those of the stomach in swine. Before the digesta enters the proventriculus, the ingested feed is held in the crop to moisten it and allow for fermentation by several *Lactobacillus* and *Bifidobacterium* species (Borda-Molina, Seifert and Camarinha-Silva, 2018; Svihus, 2014). The proventriculus acidifies ingested feed and the gizzard has a strong muscular system for thoroughly mixing ingested feed and reducing particle size. The pH of digesta in the proventriculus and gizzard ranges from 3.5 to 4.5. Similarly to swine, secretion of pancreatic juice elevates the pH to a range of 5.5 to 6.5 in the proximal small intestine.

The small intestine is where the majority of nutrient digestion and absorption takes place, and consists of the duodenum, jejunum and ileum. Pancreatic and biliary digestive juices are secreted into the duodenal lumen. The bicarbonate buffer in pancreatic juice neutralizes the low pH of gastric digesta. In addition to the extensive amount of digestion that takes place there, the duodenum also contains a highly sensitive system for monitoring and controlling of nutrient absorption and microbes. The jejunum is the main site where further and final digestion, and the uptake of nutrients takes place. Reabsorption of bile salts occurs in the ileum. The ileum also serves as extra capacity for nutrient and water absorption. Undigested material enters the caecum and colon for fermentation by a complex microbiome. Various microbial metabolites, including short-chain fatty acids, are absorbed in the caecum and colon. The caeca of birds are located at the ileal-rectal junction and are found in pairs in almost all birds, including broiler chickens, layers and turkeys.

An important difference between poultry and swine is the ability of poultry to reflux, moving the digesta up and down the small intestine. In this way, birds are able to retain the digesta for a longer period of time and bring it into more intense contact with the mucosal surface. In addition, birds have two caeca in which to allow fermentation instead of one, although only part of the digesta will enter the caeca, depending on its particle size. The fermentative capacity is relatively low in broilers and layers compared to swine. The pH in the caeca ranges from six to seven.

In ruminants, ruminal fermentation of ingested feed occurs prior to acidification and hydrolysis. The use of microbes that effectively ferment non-digestible carbohydrates allows the ruminant to make use of highly fibrous feed. Ruminants have three dedicated organs for this function: the rumen, the reticulum and the omasum. The main 'vessel' for fermentation is the rumen, which contains a highly diverse microbiome combined with papillae at the surface of the rumen mucosa to absorb SCFAs. During the process of rumination, the animal regurgitates the contents of the rumen and masticates it a second time to reduce particle size before returning it to the rumen. The reticulum serves as an intermediate staging organ, collecting smaller digesta particles and moving them into the omasum, while the

FIGURE 1
Schematic representation of the digestive systems of swine, poultry and ruminants.



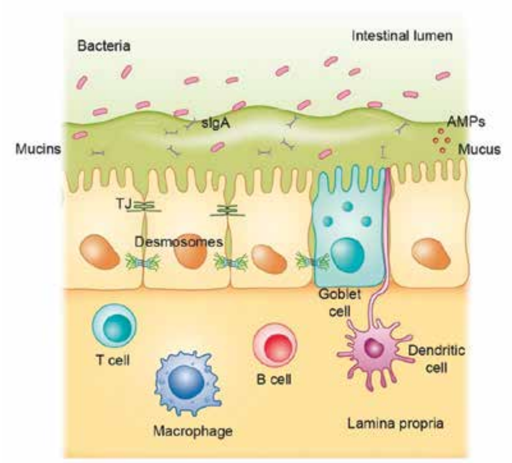
Source: Figures created by F. Brinke on behalf of the authors of this report larger particles remain in the rumen for further digestion. The pH range in the rumen, reticulum and omasum is six to seven. The omasum absorbs water and electrolytes for re-use. The SCFAs released and absorbed along the entire gastrointestinal tract are essential for meeting the ruminant's nutrient requirements. Thereafter, the principles of digestion and absorption for nutrients in the abomasum and the small and large intestine are similar to those found in swine and poultry. The pH ranges in the small and large intestines of these species are also comparable.

The host produces and secretes a wide variety of compounds with antimicrobial properties into the GIT in order to maintain the balance of the microbiome. Examples of these compounds include hydrogen chlorine in gastric juice, lysozyme in saliva, bile salts in bile, and antimicrobial peptides and immunoglobulins in pancreatic juice and mucus (Begley, Gahan and Hill, 2005; Corfield *et al.*, 2001; Hofmann and Eckmann, 2006; Joyce *et al.*, 2014; Mukherjee and Hooper, 2015; Rubinstein *et al.*, 1985). Chewing, peristalsis and motility of the GIT ensure the proper mixing of digesta with these antimicrobial secretions, as well as their transit. Furthermore, a mucosal barrier allows for final digestion and the uptake of nutrients from the lumen, while simultaneously preventing pathogenic microbes from attacking to and/or invading the body (Sansonetti, 2011). This barrier also protects the mucosa from excessive exposure to digestive enzymes and gastric acid in the foregut. The first barrier is composed of the mucus layer, the embedded commensal microbiome, secretory compounds with antimicrobial properties such as antimicrobial peptides (AMPs), and immunoglobulins (Clavijo and Flórez, 2018; Corfield *et al.*, 2001; Johansson, Sjövall and Hansson, 2013; Li *et al.*, 2015). The second barrier consists of the epithelial layer of cells, which are connected to each other by tight junctions, acting as a physical barrier (Allaire *et al.*, 2018; Vancamelbeke and Vermeire, 2017). The final barrier is the mucosal immune system, which has a defence system designed to recognize, target and kill pathogens (Ahluwalia, Magnusson and Öhman, 2017; Duerkop, Vaishnava and Hooper, 2009; Johansson and Hansson, 2016; Wu *et al.*, 2012). Figure 2 illustrates the main components of the mucosal barrier.

The mucosal barrier separates the lumen of the intestinal tract from the body. The mucus layer consists of a hydrated gel formed by mucins produced by goblet cells. The epithelium consists of epithelial cells lining the intestine. Junctional complexes, including tight junctions and desmosomes, seal adjacent cells and control the permeability between cells. Various immune cells reside in the epithelium and mucosa underneath, including dendritic cells, macrophages, intraepithelial lymphocytes, T regulatory cells and B cells. Plasma cells produce secretory immunoglobulin A (IgA) transported into the lumen by internal elastic lamina (IEL). Antimicrobial peptides (AMPs) are secreted by Paneth cells into the mucus layer.

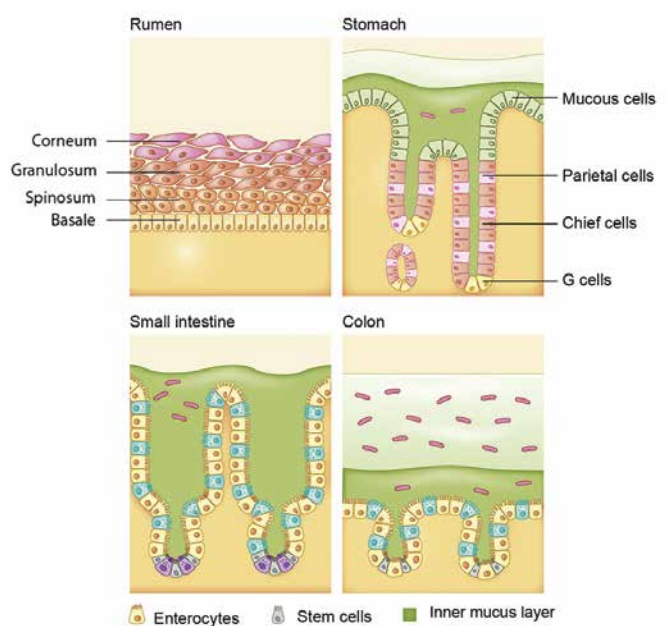
The design of the mucosal barrier differs in the various compartments of the GIT (Figure 3). The rumen, reticulum and omasum in ruminants are covered with a stratified squamous epithelium (Steele *et al.*, 2016). The epithelial and absorptive surface is increased by its structure with papillae. The top layer (corneum) acts as a protective barrier and consists of dead keratinocytes, with the granulosum, spinosum and basal layers below. Microbes colonize the corneum but do not penetrate the deeper layers. No mucus-producing cells are present. The main function of the epithelial cells is to absorb SCFAs.

FIGURE 2
Schematic representation of the composition of the epithelium and mucus in different sections of the gastrointestinal tract.



Source: Vancamelbeke and Vermeire, 2017.

FIGURE 3
Schematic representation of the composition of the epithelium and mucus in different sections of the gastrointestinal tract of ruminants, swine and poultry.



Source: Adapted from Johansson, Sjövall and Hansson, 2013; Steele *et al.*, 2016.

The stomach in swine, the proventriculus in poultry, the abomasum in ruminants, and the small intestine and colon, are covered by a single-layered columnar epithelium containing absorptive epithelial cells, mucus-secreting cells, immune cells and enteroendocrine cells. The stomach is rich in mucus-producing cells and secretory cells. Surface mucus cells produce mucus and bicarbonate, parietal cells secrete gastric acid, chief cells release pepsinogen and chymosin, and G cells secrete gastrin. The mucus is double layered, with a loose outer mucus and a dense attached inner mucus. Sodium bicarbonate is secreted into the mucus to create a microenvironment pH of five to six, protecting the epithelial cells from exposure to low pH. The epithelial cells also produce pepsin, lipase, gastric acid, bicarbonate and mucus, and are present in a single layer. There are only a limited number of immune cells present.

The small intestine is covered with a relatively thick single layer of flexible mucus, becoming denser and inflexible ('unstirred') closer to the mucosal surface. The epithelial layer has: i) enterocytes, with brush border enzymes and transport mechanisms to digest and absorb nutrients; ii) goblet cells to produce mucus, and iii) a relatively high number of immune cells which play a role in immune surveillance and response, such as M-cells and dendritic cells. The small intestinal barrier recognizes potential pathogens and secretes host-defence peptides and immunoglobulins. It is relatively rich in absorptive, immune and enteroendocrine cells, as well as Paneth cells secreting antimicrobial peptides.

The large intestine has, like the stomach, a double-layered mucus. The loose outer mucus layer is the habitat of commensal bacteria. The inner mucus layer is dense and firmly adhered to the epithelial cells. It serves as a physic-chemical barrier to prevent bacteria reaching the epithelial surface. Epithelial cells include enterocytes, which have the capability to absorb nutrients from fermentation, goblet cells and immune cells. Immune cells are present in lower numbers in the large intestinal mucosa compared to the small intestine. Due to this diverse and concentrated population of such specialized cells, along with the associated mucous layer, the intestinal tract is often referred to as the largest immune organ in the body.

DEVELOPMENT OF THE DEFENCE SYSTEM IN YOUNG ANIMALS

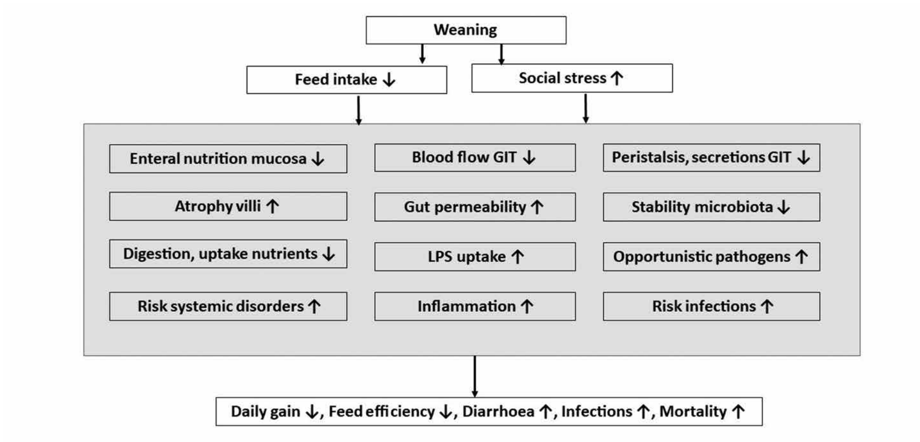
The digestive and immune systems need to develop in young animals after birth or hatch, which puts them at risk when exposed to challenges. The transfer of immune competence from mother to offspring via passive immunization is critical for health in early life. Piglets and calves will acquire passive immunity via immunoglobulins transferred via colostrum, and broiler chickens via the yolk sac (Hamal *et al.*, 2006; Rooke and Bland, 2002; Weaver *et al.*, 2000). In addition to immunoglobulins, a variety of microbiota-modulating immune-active compounds and stimulating growth factors are present in colostrum and yolk, such as oligosaccharides, bioactive amines and peptides (Stelwagen *et al.*, 2009; Xu *et al.*, 2002). Sufficient intake of colostrum is critical for immune competence and health in later life. During the birth or hatching process, neonates will also start to develop their microbiome. Over the course of these first critical days, the animal will need to learn and tolerate compounds from their diet and environment. It must learn which microbes can be identified as 'friendly' and which need to be fought (Bauer *et al.*, 2006; Mach *et al.*, 2015; Round and Mazmanian, 2009).

The immune system needs to develop quickly, since the passively acquired immunity from the mother is only available for a limited period of time: approximately four weeks after birth in piglets and calves, and two weeks after hatch in broilers (Simon, 2016). Although the young animal is already equipped at birth or hatch with an innate (non-specific) immune system, it has to quickly develop a specific immune system that more effectively targets specific pathogens (Lammers *et al.*, 2010; Stokes, 2017). Prior to this, young animals face an 'immunity gap': passive immunity is reduced and the animal's own immune system is not yet fully capable of combating pathogens. In piglets, the timing of this gap overlaps with the period of weaning, which typically takes place between three to four weeks of age. In broilers, the period of two to three weeks of age is a more sensitive period for gastrointestinal and respiratory diseases. In addition to limited immune competence, the digestive system is still immature, especially in piglets and calves. The production of digestive secretions and the control of the passage of digesta is not yet fully developed. The intestinal microbiome undergoes radical changes in the first days of life and is not yet fully established and diversified in the first weeks of life (Borda-Molina, Seifert and Camarinha-Silva, 2018; Kers *et al.*, 2018; Konstantinov *et al.*, 2006; Oakley *et al.*, 2018). As a result, young animals are particularly vulnerable to the occurrence of dysbiosis.

DYSBIOSIS

Dysbiosis can be defined as any deviation in the composition of resident commensal bacteria from that of a healthy individual (Petersen and Round, 2014). Strategies to prevent dysbiosis are fundamental to reducing the need for antibiotics. Any impairment in one of the key functions of the gastrointestinal digestive or defence systems may lead to dysbiosis (Carding *et al.*, 2015; Teirlynck *et al.*, 2011). This is often the result of stressful events such as sudden exposure to environmental changes, social stress, heat stress, parturition, exposure to high loads of pathogenic microbes (infection pressure) or inadequate nutrition (Moloney *et al.*, 2014). Such challenges may affect the normal functioning of the GIT and mucosal barrier function. A significant reduction in feed intake and reduced blood flow to the GIT, such as is the case with parturition, heat stress or weaning with piglets, can cause hypoxia and an increase in oxidative stress in the mucosa. Peristalsis and digestive secretions are reduced. Subsequent events include an increase in GIT permeability, disruption of commensal microbiota and inflammation (Lallès *et al.*, 2007; Spreeuwenberg *et al.*, 2001). Changes in the composition and diversity of the microbiome have recently been associated with performance losses and inefficiency in broilers and pigs (Lu *et al.*, 2018; Stanley *et al.*, 2013a, 2013b; Torok *et al.*, 2011, 2013). Opportunistic pathogens may colonize parts of the GIT, resulting in a subclinical or clinical disorder or disease. The most relevant dysbiotic situations in swine, poultry and ruminants occur in young animals at the critical transition periods of birth or hatch, weaning or relocation to another environment. Sows and cows are also more susceptible to dysbiosis around the time of parturition, increasing the risk of developing infections not only in the GIT, but also in the udder and uterus (Contreras, Kirkwood and Sordillo, 2013; Maes *et al.*, 2010). A schematic representation of the gastrointestinal changes that may occur after the weaning of piglets is presented in Figure 4.

FIGURE 4
Gastrointestinal responses of piglets to weaning that may lead to performance losses, diarrhoea, disease and mortality.



Source: Adapted from Pluske, Turpin and Kim, 2018; Spreeuwenberg *et al.*, 2001.

Dietary toolbox to support gastrointestinal defence

There are various dietary measures that can be taken to support the healthy functioning of the GIT and host defence. Water and feed safety and quality, feeding management, the form the feed is provided in (e.g. pellets), the composition of the diet and the use of various feed additives are all tools that can be used to support health. In general, such measures follow principles that are applicable across species.

WATER ALLOWANCE AND WATER QUALITY

The consumption of water of an appropriate quality for the animals being produced is a prerequisite for animal health. The daily water requirement of farm animals is mainly dependent on the level of feed intake, feed composition, production level, exercise and the thermal environment, including both temperature and humidity. Animals that are under stress or diseased must have continuous access to water from a welfare and well-being point of view. Insufficient water intake can lead to further deterioration of health and may delay recovery after a challenge. Poor water consumption in sows immediately following parturition has been associated with impaired milk production and reduced piglet growth (Fraser *et al.*, 1993). Weaned piglets, for example, may have difficulties in the first days after relocation to adapt to a change of drinking water system, which may be a reason for high variability in water and feed intake and prolonged weaning stress. Indeed, during the first four to six days post-weaning, the normally close relationship between feed and water intake is lost, and the presence of diarrhoea is not necessarily associated with increased water consumption (McLeese *et al.*, 1992). Regular checks of the drinking water supply and ensuring easy access to water is therefore an essential element of good farming practices aimed at reducing the use of antibiotics. Even when water is made freely available to animals, intake may not be adequate to fully meet their physiological needs (Fraser *et al.*, 1993). When animals are bored, hungry or stressed, however, they may consume excess quantities of water, often referred to as luxury consumption (Schlink, Nguyen and Viljoen, 2010).

The control of water quality is another essential element of good farming practices. Excessive levels of potential pathogens and chemical pollutants in the water are a clear risk to animal health. High levels of sulphate (>500 mg/L) in drinking water are a unique case in terms of animal health. Sulphate is well absorbed by the pig, but is re-secreted back into the large intestine where it exerts a strong osmotic effect. This leads to osmotic diarrhoea, which presents as highly watery faeces, but appears to have no other adverse effect (Patience, Beaulieu and Gillis, 2004). Chemical and microbial water quality standards for human drinking water are commonly provided by national authorities (WHO, 2017b, 2018), but national water quality regulations for farm animals are much less common.

Disease-causing bacteria, viruses or parasites may be present in the water. Some bacteria and fungi may form biofilms in the drinking water system, making them more persistent when biocides are used during cleaning. The general microbial indicators used to assess the quality of drinking water include total bacteria and coliforms, and faecal coliforms, which are indicative of contamination from waste (Figueras and Borrego, 2010). Depending on the nature of suspected clinical cases, however, the microbial testing of the drinking water may be extended to include other potential pathogens, including viruses and protozoa.

Water quality standards for swine, poultry and ruminants based on the advice of experts and veterinary health service authorities are listed in Table 1. The risk of microbial contamination is higher in surface water compared to groundwater, although groundwater is not immune to contamination (Olkowski, 2009). Risk is reduced when using potable water whose quality is controlled by national competent authorities. However, water reservoirs on farms located in relatively warm environments may provide the ideal conditions for bacterial growth, and thus need to be strictly monitored and controlled using treatments.

It should be noted that while groundwater may change in quality over time, surface water is much more susceptible to variation. These changes can occur as a result of the cumulative effects of rainwater and surface run-off, as well as evaporation. Consequently, the quality of surface water must be monitored with much greater frequency than groundwater.

TABLE 1
Water quality indicators related to the risk of microbial contamination.*

Quality criterion	Acceptable range guidance	Comments
Total bacteria, CFU/ml	<1000	Total bacteria are indicative of total system cleanliness. High numbers do not necessarily mean bacteria are harmful. Coliforms must be below a specific level.
Total coliforms, CFU/ml	<100	
Faecal coliforms, CFU/ml	0	Presence of faecal coliforms is indicative for contamination by excreta.
Potential pathogenic microbes	In general non-detectable levels are preferred	Option to assess presence of harmful bacteria, viruses, parasites. Choice will be dependent of suspected health, food safety issues.

* Adapted from GD Animal Health, 2018; Watkins, 2015; WHO, 2017b, 2018.

Regular sanitation of water storage and delivery systems using disinfecting agents is important for controlling water quality. Various forms of chlorine, as well as hydrogen peroxide and other sanitizers, are commonly used for water treatment. The use of organic acid blends supplemented to drinking water is also a common measure in programmes to reduce the use of antibiotics.

Acidification of drinking water is typically carried out during critical transition periods in piglets and broilers to further ensure water hygiene, control microbial growth in drinkers and feeders, and reduce the risk of gastrointestinal disorders. The ingested acids have a prolonged activity in the GIT, which may assist in reducing pathogen loads in the proximal intestinal tract (Canibe *et al.*, 2001; FEFANA, 2014; Hansen *et al.*, 2007; Suryanarayana, Suresh and Rajasekhar, 2012). Acidification of drinking water may also help control *Salmonella* spp. in swine and poultry (van der Wolf *et al.*, 2001). The dose of acids needed to reach a specific target pH for the drinking water will depend on the alkalinity of the water. The use of appropriate acid dosing systems and strict adherence to dosing guidelines is a prerequisite.

FEED SAFETY AND QUALITY

There are several measures needed to ensure feed safety and quality. These include minimizing the presence of microbiological, chemical and physical hazards; ensuring appropriate levels of available energy and nutrients to meet animal requirements; and physical characteristics such as particle size, pellet durability and hardness. Risk management in relation to the safety of feed and feed ingredients is an essential part of good feed manufacturing practices. The manual of Good Practices for the Feed Sector published by FAO and the International Feed Industry Federation (IFIF) provides comprehensive information on how to ensure feed safety aiming at the safety of animal-source food (FAO and IFIF, 2020). The use of alternative feed sources and agro-industrial co-products is sustainable and often economically and environmental attractive, but may also involve additional risks in terms of varying nutritional value and the presence of potential pathogenic microbes or mycotoxins (Crawshaw, 2003). Measures to control feed and feed ingredients safety and quality are typically part of a quality assurance scheme based on Hazard Analysis and Critical Control Points (HACCPs), which need to be strictly followed. A few examples follow.

Efforts to eliminate *Salmonella* spp. from feed and feed ingredients commonly rely on reducing e the risk of bacterial contamination (Crump, Griffin and Angulo, 2002; Jones, 2011). Control measures taken by feed producers include assuring the absence of *Salmonella* in purchased feed ingredients, high temperature treatment and the use of antimicrobial agents are (AFIA, 2010; FAO & IFIF, 2010). Other measures include sanitation and cleaning of the feed plant, pest, dust and moisture control, and managing the risk of contamination during storage and transportation. Processing temperatures above 80 °C are used in feed manufacturing to kill *Salmonella*, but the actual time and temperature needed is dependent on the material matrix and the processing methods applied. Formaldehyde or organic acid-based products are the most common antimicrobial agents used by the feed industry to improve feed hygiene. Formaldehyde treatment is highly effective at a relatively low cost (Jones, 2011; Wales, Allen and Davies, 2010), but there are concerns over its safety. The European Commission recently decided to ban the use of formaldehyde, their reason for doing so being that the advantages of formaldehyde do not outweigh the potential health risks associated with potential exposure while handling it. Organic acids with antimicrobial and preservation properties, such as formic acid, can be used as an alternative to formaldehyde. Of the available organic acids, formic acid has a relatively low pKa value and low molecular weight, and has been shown *in vitro* and in raw materials and feed to be highly effective at lowering counts of *Salmonella* spp. and *Enterobacteriacaea* (FEEDAP and EFSA, 2015; FEFANA, 2014). The corrosiveness of organic acids is a potential disadvantage, and suppliers often buffer organic acid-based blends to limit this effect.

More recently, concerns have been voiced over the way in which feed may act as a vehicle for the transmission of pathogenic viruses such as porcine epidemic diarrhoea (PED) and African swine fever virus (ASFV). African swine fever virus is particularly troubling, as it affects both national swine industries (in terms of their ability to trade globally) and individual farms. Protocols are being developed to address the problem, including for ingredient sourcing, manufacturing equipment and the control of movement of people and vehicles in and around feed manufacturing facilities (Cochrane *et al.*, 2016).

Mycotoxin control is another key element in feed safety, both for animal-source food safety and animal health. Mycotoxins may have a detrimental impact on the mucosal barrier function in animals (Akbari *et al.*, 2017; Antonissen *et al.*, 2015; Basso, Gomes and Bracarense, 2013; Pierron, Alassane-Kpembi and Oswald, 2016). The best strategy is to avoid contamination of feed by frequently monitoring high-risk ingredients using quality assurance schemes and strictly regulating maximum mycotoxin levels in feed. The main mycotoxins of concern in animals are the *Aspergillus* toxins aflatoxin B1 and ochratoxin A, and the *Fusarium* toxins deoxinevalenol, zearalenone, fumonisin B1+B2, and the sum of T-2 and HT-2 toxin (Pinotti *et al.*, 2016; Table 2). *Aspergillus*-derived mycotoxins are frequent in hot, humid climate regions, whereas the *Fusarium* mycotoxins can occur in all climate zones (Paterson and Lima, 2010). During certain seasons, there is a high prevalence of mycotoxin-contaminated crops, and producers may want to use contaminated raw materials for economic reasons. One option to reduce the adverse effects of mycotoxins is to use the contaminated ingredient with animal species and/or categories that are at low risk (e.g. older animals and non-breeding animals), and at levels of inclusion far below those which can cause adverse effects. Another option is to use mycotoxin-ameliorating products (Dänicke *et al.*, 2004; EFSA, 2009; Frobose *et al.*, 2017; Galvano *et al.*, 2001; Patience *et al.*, 2014). Overall, prevention of mycotoxicosis caused by feed contamination is a better strategy than treatment.

Very little is known about the effects on animals of feed contaminated with multiple mycotoxins. The standards described in Table 2 assume the presence of only one mycotoxin. Natural contamination of grains can often lead to the presence of more than one toxin, in which case lower levels may lead to growth and health impairment (Grenier *et al.*, 2011).

Due to the importance of feed being as free as possible from hazards, the proper handling, transportation and storage of feed is also of great importance. Losses may occur due to infestation with rodents and insects, the effects of birds and wildlife, and spillage (Alexander *et al.*, 2017; Yasothai, 2019).

TABLE 2
Maximum levels for mycotoxins in complete feed for swine, poultry and ruminants.

Mycotoxin	Maximum level in complete feed*	Comments
Aflatoxin B1, mg/kg	dairy: 0.005 calves, lambs, piglets, poultry starter: 0.01 beef cattle, sheep, goat, other poultry, sows, grower and finisher pigs: 0.02	Maximum levels in dairy are relatively low to avoid contamination of milk. Negative impact on mucosal barrier and liver function.
Deoxynivalenol, mg/kg	pigs : 0.9 calves & lambs: 2 other categories: 5	Swine are relatively more sensitive. Feed refusal. Negative impact on mucosal barrier function.
Zearalenone, mg/kg	piglets and gilts: 0.1 sows and fattening pigs: 0.25 calves, dairy cattle: 0.5 other categories: no maximum guidance	Swine are relatively more sensitive. Negative impact on fertility.
Ochratoxin A, mg/kg	pigs: 0.05 poultry: 0.1 other categories: no maximum guidance	Swine and poultry are relatively more sensitive. Negative impact on protein metabolism and kidney function.
Fumonisin B1+B2, mg/kg	pigs: 5 poultry, calves & lambs: 20 adult ruminants (>4 months): 50	Swine are relatively more sensitive. Negative impact on mucosal barrier function and edema in lungs.

*Derived from European Commission, 2006; GMP+ International, 2018; Pinotti *et al.*, 2016

FEEDING LEVEL

Sudden changes in feeding levels should be avoided to prevent disruption of the 'steady state' in the GIT. A consistently high feed intake is desired, as it will promote all digestive processes and related control functions for GIT health. *Ad libitum* feeding is preferred. Animals fed *ad libitum* will self-regulate their feed intake pattern. However, there is a risk that animals may overeat after a period of feed restriction prior to full recovery of the GIT (Ball and Ahernet, 1987). In such cases, small reductions in feeding levels compared to *ad libitum* feeding over the course of a few days may relieve stresses on the GIT. However, this practice may have some pitfalls. Hungry animals may become stressed and express agonistic behaviour. There is also the risk that animals will overeat once access to feed has been fully restored. Moreover, there is the risk of productivity losses: lower feed intake will result in reduced daily gain. An alternative option is to manage daily feed intake behaviour and patterns using the lighting regime. Shorter durations of lighting may slightly reduce feed intake in a more self-controlled manner, thereby reducing agonistic behaviour and mortality, and improving the health status of the animal (Brickett *et al.*, 2007). Such practices, applied for a short period of time with the priority being to promote health, should not result in a major impact on productivity.

FEED FORM AND PARTICLE SIZE

Ad libitum feeding of mash instead of pellets is an option for swine and poultry, and may be used to reduce the incidence of diarrhoea or wet litter. Mash slows down the rate of intake, reduces meal size, and increases the number of meals per day (Lv *et al.*, 2015).

Thus, similarly to restricting feed, feeding mash reduces stress on the GIT. A clear disadvantage of mash, however, is that it may lead to more spillage of feed and may reduce daily gain and/or feed efficiency in swine and poultry (Amerah *et al.*, 2007a; Laitat *et al.*, 2004; Vukmirović *et al.*, 2017). Crumbling pelleted feed is another option that allows the disadvantage of mash feed spillage to be avoided. The effect of mash, pellets or crumbled pellets on feed spillage is, however, very much dependent on the design and management of the feed delivery system.

In addition to feed form, particle size distribution in pellets and mash may affect health and performance. Increasing particle size reduces stomach lesions and ulcers in swine, and promotes the functioning of the proventriculus and gizzard in poultry (Amerah *et al.*, 2007b; Wondra *et al.*, 1995). Feeding swine and poultry mash or pellets with coarsely milled cereals decreases the risk of colonization of the GIT by *Salmonella* (Hedemann *et al.*, 2005; Visscher *et al.*, 2009). However, larger particle size also may lead to reduced digestibility and poorer feed efficiency (Wondra *et al.*, 1995).

PROTEIN

Reducing the protein level of swine and poultry feed has been shown to result in fairly consistent benefits for gastrointestinal health, such as reductions in the incidence of diarrhoea in piglets (Heo *et al.*, 2008; Wellock *et al.*, 2006) and improvements in litter quality in broiler chickens (Collett, 2012; Ferguson *et al.*, 1998). Lowering protein content, whilst maintaining critical digestible amino acid levels for performance, reduces the amount of protein entering the hindgut, thereby diminishing the risk of excessive protein fermentation by proteolytic bacteria (Gilbert *et al.*, 2018; Htoo *et al.*, 2007). Proteolytic fermentation increases production in the GIT of toxic metabolites such as branched-chain fatty acids, indoles, phenols, ammonia and biogenic amines (Bikker *et al.*, 2006; Nyachoti *et al.*, 2006). Pathogenic strains such as *Escherichia coli* and *Clostridium perfringens* may benefit from a protein-'enriched' substrate or alkaline environment (pH values >7) in the distal tract as a result of increased ammonia formation (Drew *et al.*, 2004; Heo *et al.*, 2009; Opapeju *et al.*, 2009).

Although the strategy of reducing protein content to improve GIT health is well accepted in swine and poultry, it has been less thoroughly explored in ruminants. The main focus in dairy cow and beef nutrition has been on the effect of protein level, composition and availability in the rumen, as protein supply to the ruminant is derived from rumen microbial protein and rumen-escape protein which is absorbed in the small intestine. The potential negative impact of protein fermentation in the large intestine has not been addressed.

In addition to protein levels, protein sources are also relevant when it comes to gastrointestinal health. The important criteria in swine and poultry are overall ileal or faecal digestibility, digestion and absorption rates in the proximal intestinal tract (related to risk of indigestion in a compromised GIT), the presence of possible anti-nutritional or allergenic factors, and consistency in terms of quality. From a protein digestibility point of view, some animal-derived proteins, such as casein and blood plasma, seem to be superior as far as the rate of digestion and ileal digestibility are concerned compared to the majority of plant-derived proteins (Makkink *et al.*, 1994). To overcome this, at least partly, high temperature treatment, hydrolysis or fermentation may improve the digestibility of plant proteins and reduce the presence of anti-nutritional and allergenic factors. In general, protein sources with a high rate of protein digestion and apparent ileal digestibility are used in animal diets to prevent gastrointestinal disorders.

STARCH AND SUGARS

Digestible carbohydrates in the form of starch and digestible sugars are quantitatively the most important energy source in swine and poultry feed. In a diet based on cereal grains and containing around eight percent neutral detergent fibre (NDF), approximately 65 percent of the net energy comes from starch, while in a diet containing more fibrous ingredients with NDF in the range of 15 to 17 percent, starch provides 55 to 60 percent of the total net energy. From a gut health perspective, starch is also a relatively safe source of energy. The ileal and faecal digestibility of starch usually exceeds 90 percent in swine and poultry. Furthermore, the ability to digest starch and absorb sugars is less affected by compromised GIT conditions than the ability to digest protein, fat and fibre. Nutritionists may therefore include a minimum for starch and enzymatically digestible sugars in the diet at the expense of dietary fat and fibre.

Calves, however, have a lower capacity to digest starch in their first few weeks of life than swine and poultry. Calves have a starch digestibility of around 80 percent, depending on the levels and types of starch found in their diet (Hill *et al.*, 2016; Huber, Natrajan and Polan, 1968). High levels of starch may therefore be a risk factor for fermentative diarrhoea in calves. In calf milk replacers (CMRs), lactose is used as a highly digestible carbohydrate source with a digestibility of approximately 95 percent. Additionally, piglets weaned at an age of less than three weeks still require a high amount of lactose in their diet in the first one to two weeks post-weaning. The benefit of this may not be as great for piglets weaned at higher ages (Molino *et al.*, 2011) in combination with creep feeding pre-weaning. Piglets quickly develop a high capacity to digest starch, and lactase activity decreases after weaning, especially as the level of lactose in the diet declines. However, lactose may have prebiotic properties and promote commensal bacteria such as *Lactobacillus* spp. (Pierce *et al.*, 2007). Lactose is a non-digestible oligosaccharide for poultry due to a lack of endogenous lactase, and it is therefore only occasionally included up to a total of three percent in broiler starter diets due to its prebiotic effects (Tellez *et al.*, 1993; Alloui and Szczurek, 2017; Gülşen *et al.*, 2002).

FAT

The digestion and absorption of fat is greatly affected by disorders in the GIT. The digestion of fat containing longer chain fatty acids requires emulsification by bile, hydrolysis by lipase, the formation of mixed micelles whose stability is pH-dependent, migration to the mucosal surface, and uptake by maturated enterocytes in the villi (Bauer, Jakob and Mosenthin, 2005; Iqbal and Hussain, 2009). This process is easily disturbed by insufficient bile, unstable pH conditions, and disturbances in the absorptive capacity of the mucosa caused by, for example, atrophy of the villi (Price *et al.*, 2013). Compared to starch, apparent lipid digestibility in broiler chickens and piglets is more affected during infectious challenge conditions (Smits *et al.*, 1997). High-energy diets with high fat levels may therefore not be advised for piglets and broiler chickens in feeding programmes that aim for a reduction in the use of antibiotics, where animals may be at higher risk of gastrointestinal disorders. Medium-chain fatty acid (MCFAs) and long chain unsaturated fatty acid-based oils and fats have a higher water solubility compared to long-chain saturated fatty acid-based fats, and are more readily digested and absorbed in gastrointestinal challenge conditions such as in the post-weaning period in piglets (Cera, Mahan and Reinhart, 1989). Bile salt secretion may also explain poorer digestibility of highly saturated fats in young pigs. Bile salts help to improve the solubility of unsaturated fats in the small intestine, but bile secretion is low in young pigs and only increases with age (Harada *et al.*, 1988). Young pigs also appear to be less tolerant to high levels of free fatty acids, which should therefore be avoided in post-weaning diets (Kellner and Patience, 2017). Sources of MCFAs and long chain unsaturated fatty acids include coconut oil and soybean oil, respectively.

FIBRE

Dietary fibre is defined as carbohydrate polymers with ten or more monomeric units that are not hydrolysed by the endogenous enzymes in the human small intestine. A physiologically oriented chemical characterization of the dietary fibre method includes the separation of total dietary fibre into insoluble polysaccharides, soluble polysaccharides, non-digestible oligosaccharides, lignin and resistant starch (Dhingra *et al.*, 2012; Choct, 2015; Jha and Berrocoso, 2015; Table 3). This classification of fibres is likely to be a better predicter of how dietary fibre will behave in the GIT of swine and poultry than the fibre analytics commonly used in animal nutrition, such as NDF, acid detergent fibre (ADF) and total dietary fibre (TDF).

Inclusion in the diet of insoluble fibre sources, such as husks and brans from cereals, have bulking properties that promote peristalsis and motility in the GIT, and stimulate gastric, pancreaticobiliary and mucosal secretions. The retention time of digesta in the stomach for the purposes of predigestion and acidification is increased, and the flow of digesta through the small and large intestine is improved. The larger the particle size of the insoluble fibre source, the better its water-holding and bulking properties (Eastwood *et al.*, 1983; Stephen and Cummings, 1979). The distention, bulking and secretion-stimulating properties of fibre can be effectively used in animal nutrition to support gastrointestinal health, and will be described in more detail later when discussing the specific dietary strategies for each of the animal categories covered in this publication. The beneficial effects of insoluble fibre may not be universal, however, and may be dependent on other dietary factors. For example, the expression of at least some species of *Brachyspira* is increased in the presence of corn distillers dried grains with solubles, a commonly used feed ingredient that is rich in insoluble fibre (Wilberts *et al.*, 2014).

Soluble fibres, such as the arabinoxylans and ß-glucans in wheat, barley, triticale or rye, are readily fermentable and may increase the viscosity of the digesta depending on their gelling properties. Some benefits of including high viscous fibres in piglet feed have been reported, such as slower gastric emptying of digesta and improved protein digestibility (Fledderus, Bikker and Kluess, 2007). However, high dietary levels of soluble fermentable non-starch polysaccharides (NSPs) have also been associated with increased risk of diarrhoea in swine (Hopwood *et al.*, 2004; McDonald *et al.*, 2001; Pluske *et al.*, 1998), although the literature is not very clear on this matter, as some labs have found soluble fermentable fibre to have beneficial effects during an enterotoxigenic *Escherichia coli* (infection Li *et al.*, 2018a).

TABLE 3
Simple chemical classification of dietary fibre, physical properties and general physiological effects in the gastrointestinal tract (GIT) on digesta retention time, endogenous secretions and fermentation in swine and poultry.*

Chemical class	Physical properties	Retention digesta			Effect on endogenous secretions	Fermentation rate
		Foregut	Small intestine	Hindgut		
Non-digestible oligosaccharides (number of monomeric units: 3–9)	Water-soluble, low-viscous	=	=	=	Limited	Highly fermentable
Resistant starch (RS)	Insoluble in water	=	↓ =	↓ =	↑	Readily fermentable
Soluble non-starch polysaccharides (NSP)	Water-soluble, dependent of type of polysaccharide viscous and high water-binding capacity	↑	↑ (when viscous) = (when non-viscous)	~ (variable effects reported dependent of type)	↑	Readily fermentable
Insoluble non-starch polysaccharides (classified as insoluble fibre)	Insoluble in water, (depending on type of fibre) low to high water-holding capacity	↑	↓	↓	↑	Slow to non-fermentable
Lignin (classified as insoluble fibre)	Lignin is embedded in fibre matrix. Water-holding capacity dependent on matrix properties.	↑	↓	↓	↑	Non-fermentable

↑ Increase; ↓ Decrease; = No consistent increase or decrease

* Adapted from Montagne, Pluske and Hampson, 2003; Bindelle, Leterme and Buldgen, 2008; Brownlee, 2011; Dhingra *et al.*, 2012; Kalmendal, 2012; Lindberg, 2014; Choct, 2015; Jha and Berrocoso, 2015.

In broiler chickens, high dietary levels of viscous polysaccharides may cause problems due to an undesired increase in digesta viscosity. This leads to an increase in the retention time of the digesta, slows down the rate of nutrient digestion and absorption, and may lead to an undesired increase in bacterial activity in the small intestine (Langhout *et al.*, 2000; Smits *et al.*, 1997). Excessive deconjugation of bile salts resulting in poor lipid digestibility is one of the consequences (Maisonnier *et al.*, 2003; Smits *et al.*, 1998). Mucosal barrier function can also be negatively affected, reducing resistance to opportunistic pathogens present in the GIT. To solve this problem, exogenous enzymes, such as arabinoxylanase and/or ß-glucanase, are included in feed to degrade viscous fibre structures (Bedford, 2000). This approach has been common practice in broiler nutrition for the last three decades. Piglets are less affected by viscous fibres in the small intestine due to the lower dry matter content of their digesta, thereby reducing the risk of increasing viscosity to levels that may significantly increase retention time.

Some soluble fermentable fibres, such as inulin, a poly-fructose, and sugar beet pulp containing a high level of pectic substances, have prebiotic properties and may stimulate beneficial groups of bacteria (Schiavon *et al.*, 2004; Verdonk *et al.*, 2005; Yan *et al.*, 2017). Also specific non-digestible oligosaccharides may have prebiotic effects, including fructo-, manno-, galacto- and arabinoxylan-oligosaccharides. The portion of starch that cannot be digested in the small intestine will be fermented in the hindgut, and is referred to as *resistant starch*. The rate of starch digestion in animals is dependent on granule size, the matrix structure embedding starch and the physic-chemical properties of the starch. Resistant starch is classified in human nutrition as a dietary fibre. It promotes butyrogenic bacteria in the hindgut and leads to increased production of butyric acid, which may be beneficial for gut health (Bhandari, Nyachoti and Krause, 2009; Yang *et al.*, 2017). Sources of high levels of resistant starch that can be used in animal nutrition as prebiotic fibres include native starch of legume seeds and potatoes and waxy maize. However, native legume starch will lose its resistance to digestion after thermal treatment (Sun *et al.*, 2006).

Care has to be taken in diet formulation to ensure that the total load of non-digestible oligosaccharides and fermentable fibres does not lead to excessive fermentation in the hindgut and undesired changes in the microbiome in the caecum and colon. This may result in fermentative or osmotic diarrhoea due to the excessive formation of SCFAs and other small molecular compounds. In conclusion, insoluble and bulking fibres are beneficial for GIT health in many respects, and certain prebiotic fibres could modulate at relative low inclusion level the GIT microbiome and mucosal barrier function in a desirable way. Above a certain threshold, however, soluble and viscous fibres may have detrimental effects on GIT health, which may also be dependent on the balance with insoluble bulking fibres and other dietary factors, such as levels of ileal indigestible protein (Bikker *et al.*, 2006).

CALCIUM, PHOSPHORUS AND SODIUM

Minerals are vital for many bodily functions, and in some challenge conditions or critical transition periods, mineral nutrition may require special attention. However, in contrast to other dietary measures, relatively little information is available on the impact on GIT health of providing levels of important macro-minerals such as calcium, phosphorus and sodium above nutritional requirements. In swine and poultry, high calcium levels in excess of nutritional requirements may not be desirable from a GIT health perspective. Calcium can be included in animals' diets in various forms, such as calcium carbonate (limestone), calcium phosphates or in the calcium salts of organic acids such as calcium formate or propionate. Sources of calcium with a high acid-binding capacity, such as limestone, may buffer the digesta and increase the amount of gastric acid needed to lower the pH in the stomach digesta of piglets, or in the proventriculus and gizzard of broilers, to the desired range. This potential negative effect of high acid binding capacity can generally be resolved by lowering the calcium content in the diet and using calcium sources with a low buffering capacity, such as the calcium salts of organic acids (Lawlor *et al.*, 2005).

Phosphorus is bound to phytate in plant ingredients, and a significant amount of phosphorus is therefore unavailable to poultry and swine unless phytase is added to their diet (Humer, Schwarz and Schedle, 2015). Phytate exerts also antinutritional properties by complexation with other minerals, such as zinc and calcium. The supplementation of feed with phytase releases phosphorus and the bound nutrients in the digestive tract (Walk *et al.*, 2016). Dietary modification of the phosphorus and calcium levels and the application of phytase may be applied to steer the microbial population in the different parts of the gastrointestinal tract impacting GIT health (Borda-Molina *et al.*, 2016).

However, relatively little is known about the relationship between digestible phosphorus levels in the diet and GIT health when provided at levels above nutritional requirements. Dietary phosphorus levels may affect the immune status of weaned piglets. Increasing dietary phosphorus levels was found to enhance cell-mediated immune response, but reduce humoral immune response (Kegley, Spears and Auman, 2001).

Sodium levels and water intake and retention are closely related. Moderate increases in sodium above minimum requirements will increase water intake in swine, poultry and ruminants (Bannink, Valk and Van Vuuren, 1999; Schiavon and Emmans, 2000). This could lead to wet litter in broilers, but is generally not viewed as a risk factor for diarrhoea in piglets at moderate levels above requirements. Excessive sodium in the diet is always a concern due to the risk of 'salt poisoning'; however, it would appear that if potable drinking water is readily available, the risk is low. Although the physiological and performance effects on farm animals of dietary sodium and sodium sources have been extensively investigated, relatively little information is available on the effect on gut health.

COPPER AND ZINC

The nutritional requirements of farm animals for copper and zinc are relatively low. However, copper has been shown to provide significant performance and health benefits in piglets when used at supra-nutritional dosages. Feeding piglets diets supplemented with copper up to 250 ppm significantly improves nutrient digestibility, feed intake, daily gain and feed efficiency, and reduces the incidence of diarrhoea compared to diets that only meet the minimum nutritional requirements (Dębski, 2016; Dove, 1995; Jacela *et al.*, 2010; Shelton *et al.*, 2011). The mode of action is likely to be mediated via alteration of the gastrointestinal microbiome. This might include reduced bacterial activity and a more beneficial composition and greater stability of the microbiota, which reduces the risk of colonization by opportunistic pathogens (Højberg *et al.*, 2005; Shurson *et al.*, 1990). Recent data also suggest that control over GIT hormones such as somatostatin, may be affected, and this can be directly linked to growth and satiety hormones (Yang *et al.*, 2011). The most significant improvements resulting from the use of high levels of copper in the diet take place in the immediate post-weaning period, but may also be observed in the latter stages of the nursery period. The positive effects of supra-nutritional copper levels on performance have also been reported in broiler chickens (Jegede *et al.*, 2011; Samanta, Biswas and Ghosh, 2011).

It is still common practice in many parts of the world to supplement piglet feed with zinc oxide at supra-nutritional levels of up to 3 000 ppm in order to control post-weaning diarrhoea. Its efficacy is highest in the first two weeks post-weaning; thereafter, the effect seems to be limited. Zinc oxide significantly reduces microbial activity in the GIT and also leads to alterations in the composition of the microbiota (Pieper *et al.*, 2012; Starke *et al.*, 2014; Vahjen, Pieper and Zentek, 2010). Furthermore, zinc oxide may reduce GIT permeability and reduce inflammation (Bergeron, Robert and Guay, 2014; Sargeant *et al.*, 2010). Prolonged administration of high levels zinc oxide after the first few weeks following weaning is therefore not recommended. Current advice stipulates that piglets should only be fed the highest level of zinc oxide for one week post-weaning, which should then be gradually decreased in weeks two and three. High zinc oxide levels in broiler chicken feed have been shown to be toxic (Dewar *et al.*, 1983), and zinc oxide supplementation is therefore not practised in broiler nutrition and health management.

The practice of administering high, supra-nutritional copper and zinc levels has raised concerns over its possible environmental impact (EFSA, 2010), as well as more recently, its potential connection with the development of antimicrobial resistance (Baker-Austin *et al.*, 2006; Wales and Davies, 2015). Copper and zinc at high levels may co-select antibiotic-resistant bacteria. These concerns have recently led to a decrease in the zinc and copper levels permitted in pig and poultry feed in the European Union, and the administering of high levels of zinc oxide to piglets for prophylactic and therapeutic reasons is to be banned.

VITAMINS

There are a wide range of vitamins that could be discussed here in relation to their potential role in gastrointestinal health. In general, however, defects in the digestive and absorptive system may lead to temporary vitamin deficiencies and affect gastrointestinal health. For example, the absorption of fat-soluble vitamins in weaned piglets may be impaired, since fat digestibility and absorption are affected in the immediate post-weaning period. In practice, however, the levels of vitamins fed to swine, poultry and ruminants far exceed minimum requirements, and are likely to satisfy their needs even under challenge conditions. Evidence of the supra-nutritional benefits of vitamins in terms of the gastrointestinal health of farm animals is scarce.

FEED ADDITIVES

A wide range of feed additives are available to promote gastrointestinal health. The efficacy and consistency of many feed additives can vary and are affected by feed composition, animal health, farm management, and the physical and social environment. For farmers and feed manufacturers and integrators, it can be quite challenging to choose the most effective solutions. Decisions to use certain feed additives are often based on the perceived effectiveness, mode of action, credibility of the supplier, costs versus expected benefits and their own experiences. An overview of the feed additives most commonly used to promote GIT health in swine and poultry is presented in Table 4.

TABLE 4

Overview of feed additives commonly used to promote GIT health in swine and poultry.

Products	*In vivo* effects
Various short- and medium-chain fatty acids SCFAs (<6 carbon atoms), MCFAs [6 to 12 carbon atoms]), organic acids (OAs) and inorganic acids.	Organic acids are used for preservation, but are also involved in antimicrobial activity in the GIT, and affect microbial activity and diversity (Canibe *et al.*, 2001; Dibner and Buttin, 2002; FEFANA, 2014; Khan and Iqbal, 2016; Kim *et al.*, 2005; Mroz, 2005; Partanen and Mroz, 1999; Ricke, 2003; Suryanarayana, Suresh and Rajasekhar, 2012). A wide range of organic acids can be used in animal nutrition, including formic, acetic, propionic, citric, fumaric, benzoic, lactic and sorbic acids in their various forms. The main inorganic acid used is ortho-phosphoric acid. The pH-lowering effect of acids on digesta in the first few hours after ingestion supports the barrier function in the foregut and helps prevent colonization of the GIT by pathogens (Hansen *et al.*, 2007). The bacteriostatic effect of the acids on a weight basis depends on their pKa value, solubility, molecular weight and the pH of the environment. Antimicrobial activity is mediated by reducing the pH of digesta and through the absorption of associated acids by bacteria, disrupting their metabolism and proliferation. Blending acids with different physic-chemical properties (molecular size or weight, pKa values, water solubility) may lead to additive or synergetic effects (Zentek *et al.*, 2013). At the entrance to the small intestine, organic acids are neutralized by the sodium bicarbonate in pancreatic juice, and most acids will be present in a dissociated form. MCFAs also have bacteriostatic and microbiome-modulating properties at relatively neutral pH ranges of 6 to 7 (van der Hoeven-Hangoor *et al.*, 2013; Skrivanova *et al.*, 2006), which is the pH in the proximal part of the small intestinal tract. Free MCFAs are readily absorbed in the proximal intestinal tract (Zentek *et al.*, 2011).
Products	***In vivo* effects**
Butyrate (SCFA with specific beneficial properties)	Butyrate is highly bioactive in the GIT. It increases the proliferation of enterocytes, promotes mucus secretion and may have anti-inflammatory properties (Bedford and Gong, 2018; Canani *et al.*, 2011; Hamer *et al.*, 2008). These effects suggest that it supports mucosal barrier function. Butyrate is becoming a commonly used ingredient in diets to promote GIT health.
Plant extracts, phytochemicals	Certain botanicals or nature-identical flavourings have antimicrobial or microbiome-modulating properties (Bozkurt *et al.*, 2013; Burt, 2004; Krishan and Narang, 2014; Rochfort, Parker and Dunshea, 2008; Upadhyay *et al.*, 2014). Phytogenics may also affect the functioning of the host immune system (Brenes and Roura, 2010). Administration of some of these compounds at a relatively low dose (<100 ppm) has been shown to produce significant changes in mucosal immunity (Gallois *et al.*, 2009; Liu, Ipharraguerre and Pettigrew, 2013). Phytogenics' mode of action may involve stimulation of a wide range of neuro-endocrine and immune-modulatory receptors (Aggarwal *et al.*, 2009; Furness *et al.*, 2013; Liu, Ipharraguerre and Pettigrew, 2013). Examples of phytochemicals used in animal nutrition include crude extracts of oregano, rosemary, thyme or garlic extracts, and more purified compounds thereof, such as carvacrol, thymol, cinnamaldehyde, capsaicin and allicin (Windisch *et al.*, 2008).
Direct-fed microbials (probiotics)	Probiotics in general may modulate the composition of the intestinal microbiota and the functioning of the immune system (Chaucheyras-Durand and Durand, 2010; FAO, 2016; Vondruskova *et al.*, 2010). Those most commonly used in pigs and poultry feed are *Bacillus* spp.-based probiotics, due to the heat stability of spores during pelleting (Ezema, 2013; Kenny *et al.*, 2011; Liao and Nyachoti, 2017). Another type of probiotic used is live yeasts of the species *Saccharomyces cerevisiae*. Yeasts are mainly used in dairy and beef nutrition to improve rumen efficiency and prevent rumen acidosis (Robinson and Erasmus, 2009), but can also be found in sow and piglet feed (Jang *et al.*, 2013; Jiang *et al.*, 2015; Jurgens, Rikabi and Zimmerman, 1997; Shurson, 2018). Other bacteria, such as certain *Lactobacilli* or *Enterococci* species, may be used with newly hatched or new-born animals; single or multi-strain starter cultures can be used to steer the initial microbiota in a desired direction (Liao and Nyachoti, 2017). The use of probiotics in sows may modulate the microbiome of new-born piglets (Starke *et al.*, 2013).
Prebiotics	Prebiotic sugars, non-digestible oligosaccharides (NDOs; 3–9 monomeric units) and fibres are able to modulate the intestinal microbiota selectively and stimulate specific beneficial groups of bacteria (Gaggìa, Mattarelli and Biavati, 2010; Hajati and Rezaei, 2010; Jung *et al.*, 2008; Samanta *et al.*, 2013). Examples of prebiotic sugars or NDOs include mannose, mannobiose (the indigestible disaccharide of mannose), fructo-oligosacccharides (FOSs), manno-oligosaccharides (MOSs), galacto-oligosaccharides (GOSs), transgalacto-oligosaccharides (TOSs), arabinoxylan oligosaccharides (AXOSs) and xylo-oligosaccharides (XOSs). Some sugars are able to block the binding of pathogens, such as *Salmonella* spp., to the mucosa (Ajisaka *et al.*, 2016; Oyofo *et al.*, 1989; Searle *et al.*, 2010). Mannose sugars and oligosaccharides also have immunomodulatory properties (Ibuki *et al.*, 2010; Kovacs-nolan *et al.*, 2013).

(Cont.)

Products	***In vivo* effects**
Enzymes	Exogenous enzymes can be used to break down fibres with anti-nutritional properties, and potentially also produce prebiotic sugars or NDOs (Bedford and Schulze, 1998; Kiarie, Romero and Nyachoti, 2013). Xylanase and ß-glucanase, for example, are used with broiler chickens to reduce the viscosity caused by the arabinoxylans and ß-1,3/1,4 glucans present in wheat, barley, triticale and rye, respectively. The use of xylanase and ß-glucanase may also cause oligosaccharides and sugars to be released, of which certain, for example arabinoxylan oligosaccharides, may have prebiotic properties (De Maesschalck *et al*., 2015; Niewold *et al*., 2012). In addition to fibre-degrading enzymes, amylase and protease may also be used as feed supplement to support the endogenous capacity of enzymes. In some challenging conditions, the capacity of enzymes to digest starch and protein may be reduced, for example in the first few days post-weaning for piglets. Certain enzyme blends have been shown to improve GIT barrier function (Li *et al*., 2018b).
Others	The functional ingredients described above are the most extensively described in the literature and the most commonly used in practice. Other options include, for example, antimicrobial peptides, the egg yolk antibodies of hyperimmunized hens, lysozyme, rare earth elements and clays minerals (Thacker, 2013). Clay minerals can be used to sequester toxins based on their binding characteristics and are commonly used to ameliorate the potential adverse effects of mycotoxins (Ramos, Fink-Gremmels and Hernandez, 1996; Slamova *et al*., 2011).

The range of feed additive tools available can be used to support host defence generally, to control the activity of pathogens, stabilize the microbiota and support the mucosal barrier function, for instance. However, pathogen-specific approaches can also be adopted. For example, a combined feed additive strategy can be used to reduce the risk of *Salmonella* colonization and transmission in broilers (van Immerseel *et al.*, 2006). The antimicrobial effect of organic acids such as formic, propionic or benzoic acid can be reinforced using MCFAs or phytogenic additives. Butyric acid and MCFAs were found to inhibit the expression of important virulence genes of *Salmonella in vitro* (Gantois *et al.*, 2006). Butyric acid promotes mucus secretion, increases epithelial cell turnover, stimulates anti-microbial peptide secretion, has anti-inflammatory properties, and may intervene in important colonization routes. Mannose-based sugars or oligosaccharides could act as an adhesion blocker preventing the attachment of *Salmonella* to the mucosa, and may promote IgA secretion through the modulation of macrophages (Agunos *et al.*, 2007). Direct-fed microbials can also be used immediately post-hatch for the purposes of competitive exclusion of *Salmonella*.

In any event, it is highly probable that non-antibiotic feed additives will be found to be effective under more specific circumstances than antibiotics, which have been shown to improve performance and health almost universally. This means that there is a much greater need to increase our understanding of the mode of action of these products, to ensure they are used in a way that optimizes their benefits.

Dietary strategies and options for swine

SOWS AND PIGLETS PRE-WEANING

The mother has a significant impact on the development of disease resistance and resilience in her offspring (Funkhouser and Bordenstein, 2013). In early life, disease resistance in piglets depends heavily on the passive immunity obtained from the mother's colostrum and milk. Moreover, the transfer of the microbiota from the sow to its offspring plays an important role in the development of immune competence and later-life performance (McCormack *et al.*, 2018). The uterine and vaginal microbiota of the sow will largely determine the composition of the initial microflora in her piglets. Recent findings suggest that obtaining a well-balanced and diverse microbiota from its mother helps properly develop the piglet's immune system. Any disturbance in the microbiota during the neonatal period may have a negative impact post-weaning. Piglets from sows who received antibiotics at or prior to parturition developed a less diverse and different microbiota compared to the piglets of non-treated sows. These piglets responded later in life to an immunological challenge with a more marked inflammatory response (Arnal *et al.*, 2014; Benis *et al.*, 2015; Schokker *et al.*, 2014) and seemed to have a less well developed immune competence. Strategies to promote colostrum and milk uptake, and avoiding in as far as possible the antibiotic treatment of sows, are prerequisites for a good start in life.

The condition of piglets at birth has a profound impact on neonatal performance, including colostrum intake. Recent data show how the process of parturition can result in asphyxiated piglets, and compromise their ability to survive and perform through to the nursery period (Langendijk *et al.*, 2018). Managing the condition of the sow during gestation is the first step to optimizing the parturition process, since both sows in poor condition (Vanderhaeghe *et al.*, 2010) and those in over-the standard condition (Oliviero, 2010) tend to be at greater risk of having stillborn piglets. Recent data suggest that sows may suffer from energy deficits during parturition and that ensuring feed is consumed close to farrowing will reduce both the incidence of stillborn piglets and the length of time between birthing piglets (Feyera *et al.*, 2018).

Dietary fibre and feeding level are also important tools to support the parturition process in sows. During parturition, the sow will prioritize energy supply to the muscles, and blood flow to the GIT will be reduced. This may lead to a lack of, or disrupted, motility in the GIT, constipation, increased GIT permeability leading to dysbiosis, inflammation, and conditions that promote the proliferation of opportunistic pathogens. Ultimately, this can lead to post-partum dysgalactia syndrome (PDS); when this occurs, sows typically require antibiotic treatment to support their recovery (Maes *et al.*, 2010; Martineau *et al.*, 2013). This disruption of gastrointestinal function around the time of parturition can be reduced to some extent by maintaining a relatively high fibre intake (Oliviero *et al.*, 2009). High fibre diets pre-farrowing not only alleviate constipation, but also increase intake of the lactation diet after farrowing (Quesnel *et al.*, 2009), and can improve colostrum intake, especially in low-birth-weight piglets (Loisel *et al.*, 2013). In practice, however, farmers switch from a high fibre gestation diet to a low fibre lactation diet prior to parturition; this practice is adopted to support greater energy intake, which in turn leads to increased milk production and reduced body weight loss. To avoid constipation and maintain sufficient enteral stimulation in the GIT, this switch should be postponed until after parturition. Sufficient fibre intake can also be maintained by increasing feed intake above 3 kg before farrowing. This latter strategy has been shown to have positive effects on lactation feed intake and colostrum production (Decaluwé *et al.*, 2014).

Immediately after birth, there is a period in which the immune system of piglets can be "trained" in preparation for the weaning challenge, and the GIT health in later life can be promoted (Saeed *et al.*, 2014). It is desirable that piglets be able to quickly adapt to their new situation in the post-weaning period. The first three to four weeks of postnatal life coincides with major developmental processes. The immune system of the neonatal piglet, for instance, develops in several distinct phases (Stokes, 2017; Stokes *et al.*, 2004). Feeding piglets a pre-weaning diet – either a milk replacer or a solid feed – will enhance the development of the GIT (de Greeff *et al.*, 2016). The use of the same ingredients in creep feed as are used in weaned piglets' diets will help them adapt to these ingredients. Additionally, functional ingredients may be included to support further development of the GIT; these might include prebiotic fibres, non-digestible oligosaccharides or immune-stimulating compounds to promote the development of a beneficial microbiota and immune competence.

WEANED PIGLETS

The weaning process, the stress involved and the dip in feed intake will significantly disturb the mucosal barrier function, as described in the section above on dysbiosis. This will make the piglet more susceptible to digestive system disorders and pave the way for opportunistic pathogens, of which rotavirus and pathogenic strains of *Escherichia coli* are amongst the most prevalent. Weaning is also the main period during which antibiotic growth promoters have been found to provide growth performance and health benefits, and it is therefore at this time that sub-therapeutic antibiotics are typically administered (Sneeringer *et al.*, 2015).

Lowering the crude protein content of the diet by using more digestible protein sources and synthetic amino acids has been shown to reduce the incidence of diarrhoea in piglets (Heo *et al.*, 2009; Nyachoti *et al.*, 2006; Opapeju *et al.*, 2009; Wellock *et al.*, 2006). Moreover, recent research has demonstrated that an altered amino acid ratio promotes the performance and health of pigs infected by *Escherichia coli* (Capozzalo *et al.*, 2017). During disease challenge, piglets may require higher levels relative to lysine of the essential amino acids methionine, threonine and tryptophan. In addition, some non-essential amino acids such as glutamine and glycine may enhance rapid recovery and reduce performance losses, although the veracity of this is disputed due to inconsistent experimental outcomes.

Providing more structure to the ingesta by including certain bulking fibres or larger particles in the diet can promote secretions in the digestive system and reduce retention time of the digesta in the small and large intestine (Bindelle, Leterme and Buldgen, 2008;

Jha and Berrocoso, 2015). Feeding piglets insoluble fibre sources such as husks of barley or bran of wheat was found to reduce the excretion of haemolytic *Escherichia coli* and lower the incidence of diarrhoea after weaning (Flis, Sobotka and Antoszkiewicz, 2017; Molist *et al.*, 2010; Montagne, Pluske and Hampson, 2003). The coarser the fibre, the higher the bulking properties and greater the potential for reducing this risk (Molist *et al.*, 2012). Moreover, altering the structure of the feed by coarsely milling ingredients and/or adding fibre reduces the risk of stomach ulcers in swine (Dirkzwager *et al.*, 1998). This results in a more solid, viscous structure of the digesta in the stomach, with a lower risk that the upper part of the stomach, the relatively unprotected white area in the pars oesophagus region, is exposed to acidic digesta. Soluble viscous dietary fibres may increase the retention time of the digesta in the stomach and the small intestine. This supports the acidification of the digesta and predigestion of protein (Fledderus, Bikker and Kluess, 2007). However, high levels of soluble fermentable NSPs have been associated with a higher risk of gastrointestinal infections in swine (Hopwood *et al.*, 2004; Pluske *et al.*, 1998). More recent research has suggested that beet pulp, a fermentable soluble fibre source with high water-binding capacity, may provide protection against *Escherichia coli* (Li *et al.*, 2018a). While modifications to the diet in the form of the addition of fibre afford benefits in terms of GIT health, they may also be associated with a reduced rate and efficiency of gain. In practice, therefore, these two competing objectives need to be balanced.

Non-digestible oligosaccharides (NDOs) can be used to stabilize the GIT microbiome and strengthen the mucosal barrier function. Non-digestible oligosaccharides such as fructose-oligosaccharides (FOSs) or inulin may have prebiotic properties and stimulate *Bifidobacterium* spp. and other beneficial bacterial groups (Samanta *et al.*, 2013). Other NDOs may act as anti-adhesives preventing the adhesion of pathogens to the mucosa, or promote mucosal immunity. Mannose-based sugars and oligosaccharides may bind to type 1 pili and block the adhesion of certain pathogenic gram-negative bacteria to the mucosa (Krachler and Orth, 2013; Oyofo *et al.*, 1989). Moreover, they may also activate or prime important immune cells such as macrophages and toll-like receptors (Ibuki *et al.*, 2011). However, excessive levels of readily fermentable NDOs, such as verbascose, stachyose and raffinose (the main NDOs in soybean meal), may lead to excessive fermentation in the caecum of swine and cause fermentative osmotic diarrhoea (Liying *et al.*, 2003). Overall, however, the various physio-chemical properties of fibres can be exploited in diet formulation to lower the prevalence and severity of diarrhoea in piglets. It is the amount and type of fibre, and the balance of the different fibres taken in combination with the condition of the piglet, that will determine the success of such an approach.

A special functional ingredient in relation to gastrointestinal health is spray-dried blood plasma (SDP). SDP has been shown to increase feed intake and reduce diarrhoea in weaned piglets (Bosi *et al.*, 2004; van Dijk *et al.*, 2001; Ferreira *et al.*, 2009; Torrallardona, 2010). Blood plasma contains a wide range of bioactive compounds, but it has been suggested that albumin, immunoglobulins, glycoproteins and biologically active peptides are the main fractions responsible for the reported effects (Pérez-Bosque, Polo and Torrallardona, 2016). Immunoglobulins and glycoproteins may potentially bind with the receptors of pathogenic bacteria and reduce adhesion to the mucosal wall. Moreover, SDP has been shown to improve GIT barrier function, reduce GIT permeability and decrease inflammatory responses in weaned piglets. Spray-dried egg powder derived from the eggs of hyper-immunized laying hens may be an alternative source of immunoglobulins, and also contains lysozyme, a peptide with antimicrobial properties (Oliver and Wells, 2015). Spray-dried eggs offer demonstrated benefits in relation to piglet performance and health (Thacker, 2013), although its effects may not be as consistent as with SDP (Torrallardona and Polo, 2016; Zhang *et al.*, 2015). For economic reasons, spray-dried eggs and SDP are usually only used in the first phase post-weaning in piglets and for a certain number of days as part of special starter diets for broilers. The length of time during which such products are fed will depend on the age of weaning and the weight of the piglets. For example, SDP and spray-dried eggs may be fed in greater quantities, or for a longer period of time, to the lightest five or ten percent from a weaning group.

There are a number of different feed additives that can be used to promote health. Additives with antimicrobial properties, such as organic acids, and copper and zinc oxide at supra-nutritional levels, have been shown to provide consistent benefits in piglets (Schweer *et al.*, 2017). Water and/or feed acidification may help to control microbial activity in the drinking water and feeding system, and help reduce the pH of digesta in the stomach. The efficacy of organic and inorganic acids can be further enhanced by including MCFAs or other natural antimicrobial compounds, such as phytochemicals, that engage in broad-spectrum antimicrobial activity within neutral pH ranges (Zentek *et al.*, 2013). Calcium salts of organic acids are often used in weaner diets to limit the amount of limestone in the feed, reduce its acid-binding capacity and reduce the risk of inappropriate acidification of the digesta in the stomach (FEFANA, 2014; Lawlor *et al.*, 2005). Calcium levels and calcium-to-phosphorus ratios can be relatively low in feed for weaned piglets without impairing their mineral status (Jiang *et al.*, 2013). It is important, however, to maintain a minimum level of digestible phosphorus.

Feeding supra-nutritional levels of copper, sulphate and zinc is effective in reducing the incidence of diarrhoea in the first two weeks post-weaning. High copper levels lower the microbial activity in the GIT and modulate the composition of the intestinal microbiome. It is also important to note that the mode of action of certain probiotics may include antimicrobial effects. Various Bacillus strains produce bacteriocins which engage in pronounced antimicrobial activity when confronted with relevant pathogens both *in vitro* and *in vivo*. All these ‘antimicrobial’ measures are focused on stabilizing and controlling the intestinal microbiome in piglets in such a way that the risk of the colonization and transmission of pathogens is reduced.

A second focus of feed additive interventions is strengthening mucosal barrier function. Butyrate has pronounced effects in this regard, as it increases mucus production, epithelial cell proliferation and modulation of the GIT-associated immune system (Bedford and Gong, 2018). Supplementing feed with butyrate may significantly reduce GIT permeability in piglets (Huang *et al.*, 2015). Enzyme blends have also been shown to improve barrier function in the newly weaned pig (Li *et al.*, 2018b). Various phytochemicals have been demonstrated to have immune-stimulatory and anti-inflammatory effects in piglets (Huang and Lee, 2018). These anti-inflammatory properties may be associated with antioxidant properties (Qin and Hou, 2017). Probiotics may also influence mucosal barrier function and immunity as part of their mode of action (Liao and Nyachoti, 2017). A combined feed additive strategy that aims to stabilize the microbiota, control pathogens in general and bolster mucosal barrier function is a highly desirable intervention strategy for weaned piglets.

GROWING-FINISHING PIGS

The transition of piglets from the nursery to the grower unit is another stressful period for pigs, albeit to a much lesser degree, and therefore deserves special attention when looking at ways of reducing the use of antibiotics. For this reason, some pork producers have adopted two-site (sow barn + wean-to-finish barn) as opposed to three-site (sow barn + nursery + grow-finish) production systems. Diets fed immediately after relocation to the grower-finisher unit usually contain some extra safety measures similar to those described in the piglets sections above, but at lower cost. In the first diet phase following relocation, lowering the protein content, adding more fibre structure, controlling the amount of fermentable carbohydrates and maintaining high levels of copper, possibly in combination with organic acids, are typical measures that can be applied at relatively low cost (Partanen and Mroz, 1999). Farmers also adopt this dietary approach in the final nursery phase in order to minimize the combined stress of changes in location and feed composition.

Dietary strategies and options for poultry

BROILER BREEDERS

The nutrition of broiler breeders may impact the performance and health of their offspring. Breeder nutrition needs to be optimized to support early immunity in day-old chicks and high vitality (Hocking, 2007). Dietary measures that can be adopted to achieve this include feeding them adequate nutrient levels. The use in breeder diets of functional ingredients such as n-3 polyunsaturated fatty acids, supra-nutritional vitamin levels and organic trace elements may further support immune competence in broilers (Chang, Halley and Silva, 2016; Kidd, 2003). In addition, paternal nutrition may also affect sperm quality and subsequent offspring viability (Chang, Halley and Silva, 2016). However, relatively little is known about the impact of maternal or paternal nutrition on the development of the intestinal microbiome and mucosal barrier function in broiler chickens.

BROILER CHICKENS

The first three to four weeks of life is the main period during which broiler chickens are at risk of gastrointestinal disorders and infections. At hatch, the young chickens will be exposed to a challenging environment in which their vitality, the quality of the passive immunity they received from the yolk sac, the initial development of their microbiome and their immediate access to feed and water will all be key factors in the proper development of host defence capabilities (Yegani and Korver, 2008). Under suboptimal conditions, the above-mentioned problem of dysbiosis may already occur in the first days post-hatch, and there is a potential high risk of *Escherichia coli* infections at this age (Dziva and Stevens, 2008). Modern hatching practices mean that the natural transfer of the microbiome from the mother (broiler breeder) to the offspring (broilers) is disrupted, and random exposure to the microbiota in the environment of the hatchery generally leads to lack a of control over the initial microbiome (Stanley *et al.*, 2013b). In the weeks thereafter, coccidiosis and *Clostridium perfringens* infections are the predominant causes of enteric infections (M'Sadeq *et al.*, 2015). These gastrointestinal disorders may result in wet litter, leading to additional health problems, performance losses, and carcass quality, skin and footpad damages.

Coccidiosis is a disease caused by one or more species of the protozoan parasite *Eimeria*. The infective form is the oocyst which is transmitted to other birds via the excreta. Prevention can be achieved through the use of anti-coccidial feed additives. The inclusion of ionophore anticoccidials in broiler chicken diets is common practice to prevent coccidiosis. Ionophores are structurally not related to the therapeutic antibiotics used in human and animal medicine, and are therefore classified by the World Health Organization (WHO, 2017a) as at low risk of co-selecting for antimicrobial resistance against medically important antimicrobials. In many countries, anticoccidials are regulated as feed additives and do not require a prescription from a veterinarian. The use of anticoccidials in broiler chickens to prevent secondary bacterial infections, such as necrotic enteritis caused by *Clostridium perfringens*, is recommended. Vaccination against coccidiosis can be an alternative strategy, and certain phytochemicals, such as essential oils derived from oregano, may also help prevent coccidiosis (Bozkurt *et al.*, 2013).

Immediate access to feed and water in the first hours post-hatch is critical to supporting gastrointestinal defence mechanisms. It prevents dehydration and supports gastrointestinal functions that are key to the control and development of the gastrointestinal microbiome (Uni and Ferket, 2004). Feed intake will trigger peristalsis, secretions and the release of yolk sac residues, and enhance the development of the innate immune system. Treating broiler chickens as soon as possible after hatch with probiotics, either via feed, water or spraying, is another measure that may support the development of the host defence system (Baldwin *et al.*, 2018).

The immunity gap, caused by the loss of passively acquired immune protection at a time when the broiler chicken's innate and specific immune system is as yet underdeveloped, usually occurs between weeks two and four post-hatch (Lammers *et al.*, 2010; Yosipovich *et al.*, 2015). This increases the risk of gastrointestinal disorders, and broiler birds are more prone to dysbiosis and infections. After the immediate post-hatch period, this is the second critical window during which broilers are more susceptible to infection.

The inclusion of bulking structures in the diet by adding coarsely milled cereals or coarse fibres supports the development and functioning of the proventriculus and gizzard, and improves pre-digestion of feed in the foregut. Various authors have noted the positive effects of this on nutrient digestibility and feed efficiency (Jimenez-Moreno *et al.*, 2009; Jiménez-Moreno *et al.*, 2016; Kalmendal, 2012). Similar benefits can also be achieved by including whole cereals (Gracia *et al.*, 2016; Plavnik, Macovsky and Sklan, 2002). Fibre of a soluble nature or with a fine particle size distribution seems to be less effective, indicating that it is the bulking and distention properties of fibre that produce the beneficial effects reported in broiler chickens.

A second approach is to reduce the crude protein content of the feed whilst meeting the requirements for essential amino acids. In general, this will reduce water intake and help to prevent wet litter problems (Dunlop *et al.*, 2016; Ferguson *et al.*, 1998). Additionally, it will protect the GIT by reducing the formation of ammonia and other putrefactive metabolites of the microbial degradation of protein (Qaisrani *et al.*, 2015). A diet with a high protein content is also considered to be a predisposing factor for necrotic enteritis caused by *Clostridium perfringens* (Drew *et al.*, 2004). Although reducing the protein content is an effective measure, care has to be taken that the protein content is not lowered to a level that would have a negative impact on feed intake and efficiency.

As with piglets, the partial replacement of fat as an energy source with starch is the safer option for energy digestibility when broiler chickens are exposed to pathogens (Amerah and Ravindran, 2014; Smits *et al.*, 1997). Broiler chickens have a limited capacity to digest and absorb lipids due to their relatively low concentration of bile salts, especially in the first three weeks of life (Guban *et al.*, 2006; Krogdahl, 1985). When fat is used, unsaturated fatty acids are strongly preferred to those rich in saturated fatty acids. Unsaturated fatty acids are less dependent than saturated fatty acids on bile salt action in the process of digestion, and are usually better absorbed (Smits, Moughan and Beynen, 2000; Tancharoenrat *et al.*, 2014).

Viscous non-starch polysaccharides present in cereals such as wheat, barley, triticale and rye may have detrimental effects on nutrient digestibility in broiler chickens and may cause wet litter (Choct, 2009). The increase in digesta viscosity they produce significantly increases the retention time of digesta in the small intestine, which may lead to excessive microbial activity. The main preventative measure is to supplement the diet with enzymes that reduce the viscosity of the polysaccharides (Bedford, 2000). In addition, enzymes degrade polysaccharide structures or matrices that may enclose nutrients. The most commonly used enzymes are xylanase and ß-glucanase, which degrade viscous arabinoxylans and ß-glucans, respectively.

Of the minerals that can be added to feed, calcium and sodium seem to be the most important for broilers' gastrointestinal health. Excessive calcium levels from limestone or calcium phosphate may increase the buffering capacity of the diet and may affect pH barrier function in the crop (where the usual pH range is four to five as a result of mild fermentation) and the proventriculus (Amerah *et al.*, 2014; Morgan *et al.*, 2014). Slowly soluble calcium sources may be preferable to highly soluble sources (Hamdi *et al.*, 2015; Walk *et al.*, 2012). Increasing sodium levels above minimum requirements, typically accomplished by adding sodium chlorine, may increase feed intake and daily gain to a certain level, but will also increase water intake and may lead to wet litter problems (Murakami *et al.*, 2000; Zduńczyk and Jankowski, 2014). Both calcium and sodium levels must of course meet minimum nutritional requirements.

Organic acids in feed or drinking water may also support barrier function in the foregut (Andreopoulou, Tsiouris and Georgopoulou, 2014; Chaveerach *et al.*, 2004; Dibner and Buttin, 2002; Khan and Iqbal, 2016; Ricke, 2003). Care has to be taken that feed and water intake is not affected and that the pH of feed (*in vitro*) and water is not lower than 3.5. Furthermore, a wide variety of feed additives can be used with broiler chickens to support GIT defence mechanisms The main additive categories used in addition to organic acids are MCFAs, phytogenic additives, probiotics, yeast-derived additives and prebiotic sugars (Choct, 2009; Huyghebaert, Ducatelle and Immerseel, 2011; M'Sadeq *et al.*, 2015). It is clear that a single additive cannot be seen as a silver bullet for preventing GIT disorders or infections. A combination of additives with different modes of action might be a more promising approach when it comes to reinforcing GIT defence mechanisms, with certain additives chosen to promote the stability and diversity of the microbiome and others to support mucosal barrier and immunity function.

TURKEYS

Similar dietary measures to those used with broilers can also be used to support the gastrointestinal health of turkeys. Levels of indigestible protein may need to be limited, and starch rather than fat and fibre will enhance performance under challenging conditions. A difference in the design and functioning of the GIT compared to broilers is that turkeys' ceca and fermentative capacity are more developed. A larger proportion of dietary fibre is fermented and a higher level of fibre can thus be included in the diet (Sklan, Smirnov and Plavnik, 2003). The dry matter content of the digesta is lower and the viscosity of dietary fibre is less of a problem with turkeys, although enzymes may still be required to support digestion. Measures to support gastrointestinal health through the use of fibre are similar to those advised for piglets. Insoluble fibres, preferably coarse in structure, can be used as bulking material and are preferred to soluble fibres.

LAYING HENS

In early life, the relocation of pullets to the layer farm and their transition from the rearing to the laying stage is a period of high risk in which there is greater susceptibility to gastrointestinal disorders. Floor-housed laying hens are, like broilers and turkeys, exposed to the risk of coccidiosis infections and require appropriate control measures. Subclinical coccidiosis may predispose hens to other gastrointestinal problems. As with broilers and turkeys, a variety of dietary measures can be adopted to prevent dysbiosis in laying hens, and in general these follow the same intervention strategy of supporting the host defence system and reducing the risk of gastrointestinal 'disturbances'. Reducing the protein content of layer diets will result in less protein fermentation, reducing the formation of ammonia in the GIT and decreasing ammonia levels in the environment. However, care has to be taken that amino acid requirements are met (Ribeiro *et al.*, 2016; Roberts *et al.*, 2007). Exposure to high ammonia levels may adversely affect the health and production of layers by reducing mucosal barrier function in the GIT and lungs (Kristensen and Wathes, 2000).

Including coarse insoluble fibres in the diet or coarsely milled cereals may also be beneficial for layers in terms of supporting the development and functioning of their GIT. However, evidence of the effect of this on the gastrointestinal health and performance of young laying pullets is scarce. Including coarse particles in the diets of laying hens did not improve performance per se (Mateos *et al.*, 2012; Safaa *et al.*, 2009), but other benefits have been reported, such as reduced agonistic pecking behaviour and a lower risk of fatty liver syndrome (Kalmendal, 2012; van Krimpen *et al.*, 2005).

Laying hens require a diet with relatively high calcium and phosphorus levels for eggshell formation. High dietary levels of calcium and the use of limestone increases the buffering capacity of the diet and may affect the hen's ability to reduce the pH of digesta in the proventriculus and gizzard. Avoiding excessive Ca, and limiting the limestone content in particular, is one way of preventing this problem. Another option is to use coarse limestone particles to lower the rate of dissolution, although the results from studies looking at the impact of this practice on performance, egg quality and health have been rather inconsistent (Araujo *et al.*, 2011; Guo and Kim, 2012; Świątkiewicz *et al.*, 2015). Calcium salts of organic acids are not commonly used in layers for economic reasons. Various feed additives can be used to support gastrointestinal health (Świątkiewicz *et al.*, 2013), but GIT disorders are less common in laying hens than they are in young birds. The GIT of laying hens is more developed and mature, and thus more resistant to disease.

Dietary strategies and options for ruminants

DAIRY AND VEAL CALVES

Diarrhoea is frequent in calves, and antibiotic use is relatively high. Calves will go through several critical transitions: the first takes place in the first few days after birth with the weaning of calves and rearing using either whole milk or calf milk replacer (CMR). The second occurs if calves are relocated for rearing. The third transition occurs when the animals move from whole milk or CMR to solid feeding with roughage and concentrates (Drackley, 2008). Sufficient uptake of colostrum in the first six hours after birth is important for the proper establishing of passive immunity (Godden, 2008). Ideally, colostrum feeding in combination with whole milk or CMR should continue until the calves are two to three days old. Calves should also have *ad libitum* access to water. When mixing CMR, only water of good quality should be used. CMR is best prepared in small batches, as, ideally, only freshly mixed CMR should be fed to calves. Any leftover CFR should be appropriately stored if it is to be reused. The relocation of calves, involving considerable social stress, and the change in their diet is a period during which the risk of dysbiosis is significantly elevated (Enríquez, Hötzel and Ungerfeld, 2011).

Enteric and respiratory problems peak during the first few weeks of life, despite the fact that calves receive a highly digestible diet of either whole milk or CMR derived from dairy ingredients (skimmed milk and whey powder). Adequate feed safety measures, such as pasteurization, are advised when whole milk is fed to calves, not only for reasons of feed hygiene in general, but also to prevent the transfer of diseases from the herd to the calves (Godden *et al.*, 2005). In contrast to piglets and broilers, the capacity of calves to digest starch is limited (Coombe and Smith, 1974). For economic reasons, certain plant proteins may be used, such as hydrolysed wheat gluten or soy protein isolate and concentrate, whose antigenicity and the presence of anti-nutritional factors are reduced as a result of processing at high temperatures (Lallés, 1993; Toullec, Lallès and Bouchez, 1994). In addition, manufacturers of CMR use highly digestible fat sources and methods to improve lipid solubility and digestibility, such as emulsification and spray drying (Hill *et al.*, 2009; Radostits and Bell, 1970; Raven, 1970). All these measures are required to produce a CMR that is able to support the nutritional and functional requirements of calves and to achieve the desired physico-chemical properties of the liquid diet when the CMR powder is mixed with water. In the pre-ruminant phase, a nutrition plan containing high levels of CMR/whole milk may be beneficial for performance and health (Johnson *et al.*, 2017). After the milk phase, which usually continues until the age of six to ten weeks, the calves will gradually receive more roughage and concentrate, which will stimulate the development and maturation of the rumen.

Scouring and lung infections are common health problems in young calves and one of the main reasons for antibiotic use. Infectious causes include a wide variety of bacterial, viral and parasitic infections. Dehydration is common, and rehydration solutions containing sugars and electrolytes can be used to prevent and treat this (Brooks *et al.*, 1996; Constable, Thomas and Boisrame, 2001). Additional dietary measures to reduce the incidence and severity of diarrhoea include the use of functional proteins such as spray-dried plasma or egg powder derived from eggs produced by hyperimmunized hens. These layers produce eggs with elevated levels of pathogen-specific IgY (Erhard *et al.*, 1997; Ikemori *et al.*, 1992, 1997; Quigley and Drew, 2000; Quigley, Kost and Wolfe, 2002; Vega *et al.*, 2011). However, regulatory restrictions may prohibit the use of animal co-products such as spray-dried plasma in calf milk replacers. Of the possible feed additives, pro- and prebiotics are the most commonly used in CMR to support GIT health (Timmerman *et al.*, 2005; Uyeno, Shigemori and Shimosato, 2015). Pre- and probiotics can also be combined with feed additives with antimicrobial properties. For example, acidified milk prepared using formic acid and with a pH in the range of 4 to 4.5 was found to improve GIT health in veal calves (Todd *et al.*, 2017). Moreover, supplementing milk replacer with butyric acid or butyrate has been shown to support rumen papillae development in calves (Gorka *et al.*, 2009; Kato *et al.*, 2011; Mentschel *et al.*, 2001; Sander *et al.*, 1959), indicating trophic effects similar to those observed in swine and poultry. Butyrate has also been shown to support gastrointestinal functions relating to GIT integrity and defence mechanisms in calves (Guilloteau *et al.*, 2009).

DAIRY COWS

The use of antibiotics in dairy production systems is limited. Typically, antibiotics are used to control udder health through the prevention and treatment of mastitis during drying off and early lactation (Krömker and Leimbach, 2017). A common parameter used to assess udder health is the somatic cell count (Sharma, Singh and Bhadwal, 2011). The somatic cell count includes the number of leukocytes and epithelial cells and is indicative of the immune response to bacterial invasion in the udder. Mastitis may cause significant economic losses affecting milk production, milk quality and the longevity of dairy cows (de Vliegher *et al.*, 2012). Pathogenic strains of *Staphylococcus* are often the causative infectious bacteria, with certain *Mycoplasma* spp. as a second group of emerging, potentially harmful bacteria. The incidence of mastitis is highest during early lactation; the incidence rate is higher in heifers than multiparous cows during the first ten days of lactation, after which the rate becomes higher in multiparous cows (Steeneveld *et al.*, 2008). The risk of mastitis is also higher when cows are exposed to heat stress. The incidence of mastitis is interrelated with other health issues in dairy cows, such as milk fever, ketosis, acidosis and metritis. These diseases or disorders occur during the transition phase, when gastrointestinal and metabolic challenges around the time of calving, as well as the negative energy balance during early lactation, are predisposing factors for the development of health problems (Ingvartsen and Moyes, 2013; Raboisson, Mounié and Maigné, 2014). Non-antibiotic prevention and control strategies include measures relating to housing, hygiene, welfare, management and vaccination (Gomes and Henriques, 2016). Similar to sows, the parturition process in dairy cows is a critical transition period during which a profusion of events take place that may negatively affect host defence and provide an opportunity for pathogens to cause infection (Bradford *et al.*, 2015). The reduction in roughage and concentrate intake that coincides with parturition may cause dysregulation of gastrointestinal functions, and has been associated with post-partum disorders and diseases such as retained placenta, metritis and mastitis (Conte *et al.*, 2018; Huzzey *et al.*, 2007; Luchterhand *et al.*, 2016; Rhoads *et al.*, 2009). Reduced and irregular feed intake patterns are also associated with elevated levels of inflammatory markers in dairy cows (Garcia, Bradford and Nagaraja, 2017; Min *et al.*, 2016). It is therefore recommended to include high levels of fibre from forages in the total mixed ration and maintain a consistent feeding level throughout the parturition period in order to support gastrointestinal functioning, stimulate rumination and reduce the risk of inflammation and metabolic disease.

A second area that requires attention prior to calving ensuring the cow is able to mobilize calcium from body reserves. Insufficient mobilization of calcium from body reserves around calving may lead to inadequate calcium blood levels in dairy cows, a metabolic disease known as hypocalcaemia or 'milk fever'. The highest incidence is in the first day post-partum. Milk fever may also predispose dairy cows to other disorders and diseases, including metritis and mastitis, for which antibiotic treatment may be needed. This risk can be reduced through various dietary measures, including feeding reduced Ca levels prior to calving, lowering the dietary cation–anion balance, and ensuring sufficient dietary magnesium and supplementing with calcium immediately post-partum (Goff, 2008).

After calving, the lactating dairy cow will enter a state of negative energy balance, where the nutrient demands of milk production are not met though dietary nutrient intake. Encouraging dry matter intake will help to avoid a severe negative energy balance and reduce the risk of developing metabolic diseases such as ketosis. Ketosis is caused by the excessive release of non-esterified fatty acids (NEFAs) from the liver and body fat reserves. It leads to undesired high production and the release of ketone bodies such as acetoacetate, acetone and beta-hydroxybutyrate (Andersson, 1988). A strategy of providing 'controlled-energy' diets to meet energy demands and avoiding overfeeding in late gestation can be used to programme the liver to more effectively utilize NEFAs in the immediate parturition period. However, there is also a risk of 'over-feeding' the cow with rapidly fermentable carbohydrates, which may lead to sub-clinical rumen acidosis, and hindgut acidosis (Owens *et al.*, 1998; Plaizier *et al.*, 2008). Acidosis, whether clinical or sub-clinical, is associated with a sudden rise in short-chain fatty acid (SCFA) production in the rumen and a drop in rumen pH below 5.5. The microbiota is altered and the rumen wall is not able to properly respond to the high uptake of SCFAs, resulting in metabolic acidosis. Disorders in the rumen wall and GIT epithelial barrier function prompting increased uptake of inflammatory lipopolysaccharides (LPSs) may lead to systemic problems (Plaizier *et al.*, 2012; Steele *et al.*, 2009). The risk of acidosis can be reduced by lowering the amount of concentrate feed and providing a relatively higher proportion of effective fibre in dry matter at the expense of starch, sugars and rapidly fermentable soluble fibres, along with other methods to alter SCFA production and rumen buffering (Humer *et al.*, 2017; Krause and Oetzel, 2006). Effective fibre refers to insoluble or neutral detergent fibre and fibre of appropriate particle size and length. Feed additives used to alter SCFA production and rumen pH include live yeast and buffering agents such as sodium bicarbonate (Duffield *et al.*, 1998; Erdman, 1988; Mullins *et al.*, 2012; Poppy *et al.*, 2012; Staples and Lough, 1989).

Live yeasts and buffering agents are the feed additives most commonly used in dairy nutrition. In addition to these ingredients, other feed additives may also promote gastrointestinal health. Increasing levels of vitamin E, selenium and organic trace element sources in the diets of dairy cows has been studied extensively in relation to the functioning of their immune and antioxidant system and its effect on other health-related parameters, including the somatic cell count as a marker of udder health (O'Rourke, 2009; Spears and Weiss, 2008). This could complement strategies to reduce the incidence of mastitis. Overall, the priority in terms of feeding the high-producing dairy cow during transition periods is to stabilize rumen fermentation and keep the cow healthy. This must be achieved for the most part through the proper feeding of dry cows to reach desired body condition targets at calving and an appropriate feeding strategy around the time of calving involving rations containing sufficient effective fibre.

BEEF CATTLE

With the exception of ionophores and coccidiostats, antibiotic use in beef cattle is mainly restricted to young beef calves during relocation periods. Transportation and mixing is common in typical beef cattle production systems. In the United States of America, for example, animals may move from cow-calf operations to stocker and backgrounding operations before they are placed in finishing feedlots where they stay until slaughter weight is reached (Sneeringer *et al.*, 2015). In such a system, antibiotics are mainly used to prevent and treat respiratory diseases such as Bovine respiratory disease (BRD), and their use for gastrointestinal infections is less common. Acidosis can be a problem in intensive beef farming systems where high levels of concentrates are fed, and similar intervention strategies to those described in the previous paragraph on dairy cows can be adopted (Nagaraja and Titgemeyer, 2007). Stabilizing rumen fermentation using live yeast or ionophores, and including effective fibre, have also been shown to be effective in beef cattle (Hernández *et al.*, 2014). Unfortunately, the routine administering of antibiotics to beef cattle as either a standard health management measure and/or to promote growth is still permitted in several countries but it is not advisable.

Health claims of dietary interventions

Generally, animal nutrition is regulated by animal feed legislation, and animal health interventions are regulated by veterinary legislation. A fine line separates these two legislative areas, particularly where animal nutrition solutions for suboptimal health conditions are concerned. In most jurisdictions, animal nutrition solutions intended to prevent, cure, treat or mitigate disease conditions are considered to be drugs under veterinary legislation. This not only applies to market access but also label claims. From an animal nutrition perspective, both are limitations. The veterinary registration of products and solutions is often a costly and time-consuming affair, and tends to focus on the prevention or treatment of a specific disease. Dietary measures to support gastrointestinal health and host defence are often more generic and not pathogen-specific. As a result of the current regulatory system, there is a lack of recognition of the impact of nutrition on gastrointestinal health and overall animal health and welfare. Nonetheless, the effective adoption of dietary interventions will undoubtedly lead to a reduction in the need for antibiotics. The urgency of the issue requires new regulatory approaches. Regulatory recognition of the prophylactic effects of feed additives used in animal health should further contribute towards reducing AMR (den Hartog, Smits and Hendriks, 2015). Certainly, the animal protein value chain needs a regulatory environment which is balanced to meet the needs of all those participating in it, and which also encourages the implementation of new technologies. Maintaining consumer confidence and feed-to-food safety remain the leading concern. In the event that existing feed legislation cannot be easily adapted, new legislation outside the scope of the present feed and veterinary legislation could be an option. Such changes may be time-consuming, however, as they will have an impact at both national and international levels. A regulatory option to consider, currently being explored in the European Union, would be to establish a regulatory framework that allows feed additives to make claims about their beneficial effects on animal health and welfare. Although the parameters for animal welfare enhancers under such claims are not yet defined, they could be related to improving the physiological condition of animals during critical transitions such as parturition, birth, weaning and relocation, and when exposed to environmental challenges such as heat stress. During these critical periods, performance losses and non-infectious clinical problems may occur that can be ameliorated using dietary interventions. Relevant zootechnical end-point parameters, such as daily gain, feed efficiency and milk and egg production, can be examined alongside more explanatory parameters describing changes in the microbiome, mucosal barrier function, immune response and stress levels. Moreover, visual observations such as damage to feathers and skin, as well as potentially behavioural aspects could be included in the set of parameters in order to prove the claim that animal welfare is improved. Such an approach to feed regulation would acknowledge the important role that nutrition may play in animal health and welfare, and would avoid, either entirely or almost entirely, any overlap with veterinary legislation.

Dietary best practices in programmes to reduce antibiotic use

The dietary measures described in this document can contribute to preventing disease or lessening the impact of an infection. It is not possible, however, to evaluate or ascertain the success of combinations of dietary measures, which are common in most antibiotic reduction programmes. Most studies published in the literature describe the effect of a single factor, and usually under experimental conditions that may not be representative of real-life situations. Even when researchers try to recreate real-life conditions, these can vary widely from farm to farm in terms of pathogen load and exposure, so establishing relevant research conditions is very difficult. Moreover, farmers take a multifactorial approach to biosecurity, genetics, animal health care, animal welfare, nutrition and management. Lessons can be learned, however, from the empirical approaches adopted by countries that have successfully reduced antibiotic use without compromising animal performance and health, for example Denmark or the Netherlands. Both countries have succeeded in significantly reducing antibiotic use in piglets, broilers and calves in recent years. Bulk medication of feed is either not permitted (the Netherlands) or heavily restricted (Denmark). The sub-therapeutic use of antibiotics is now forbidden in the United States of America and Canada. Driven by market demand, swine and broiler production that makes no use of AGPs and limited use of therapeutic antibiotics is growing at a rapid rate globally.

The administering of medicines has to be focused as much as possible on only treating affected animals via drinking water or individual treatment (swine). When formulating diets, nutritionists tend to include maximum levels of total protein. Coarser milling and pelleting is common practice with both swine and broilers. Use of organic acids is a standard measure for piglet feed in both Denmark and the Netherlands. It is not routine in broiler feed, where costs versus efficacy are not as consistent as in piglets. Water acidifiers are commonly used during sensitive periods for both piglets and broilers. With piglets, this is in the weeks post-weaning and following relocation to the growing-finishing unit, and with broilers, it is typically until three to four weeks of age (during the immunity gap). Other additives with antimicrobial activity, such as MCFAs and phytogenic additives, are also frequently used in feed. Probiotic and prebiotic concepts are applied as well: usually in piglets' first post-weaning diets and broiler starter diets. NSP-degrading enzymes are routinely included in European wheat-based diets for broilers. For piglets, most producers use enzymes as a safety measure in the post-weaning phase in order to support digestion, although performance improvements are known to be inconsistent. The administering of zinc oxide to piglets at 2 500 to 3 000 ppm is still a common practice in Denmark in the immediate post-weaning phase, but will be phased out in the near future due to new European Union regulations.

Most of the dietary measures for swine and poultry described in this publication are common practice in the Netherlands and Denmark; many are in common use worldwide. It has to be kept in mind, however, that farming conditions vary, and that tailor-made approaches based on thorough analysis of a specific farm's circumstances and the needs of its farmer are recommended. A multifactorial approach with clear targets, a plan, and strict monitoring and adjustment of the programme based on results, is likely to be the key to success in reducing the use of antibiotics. One of the clear differences between the sub-therapeutic use of antibiotics and its alternatives is the much broader application and effectiveness of the former. Alternatives to antibiotics tend to be more situation-specific, and greater attention must therefore be paid to accurate diagnostic procedures to ensure that the correct dietary measures are adopted.

Conclusions

Nutrition is one of the pillars of gastrointestinal health and contributes to minimizing antimicrobial use in farm animals. Various dietary strategies and options for swine, poultry and ruminants that can be used as building blocks or tools to achieve targets in animal health, production efficiency and reductions in antibiotic use have been discussed. A summary of these dietary strategies is provided for piglets, broilers and calves in Tables 5, 6 and 7, respectively. These young animals are at the highest risk of needing antibiotics for prophylactic or therapeutic reasons. The main objective of nutritional intervention strategies is to support or strengthen host defence. The animal already possesses an ingenious system for combatting pathogens whilst allowing efficient digestion and absorption of nutrients. Gastrointestinal motility, digestive secretions, the microbiome, the mucosal barrier and the immune system all play important roles in host defence, and all can be effectively supported through nutrition. Dietary measures adopted alongside biosecurity, genetics, animal health care, animal welfare and farm management are the keys to success in improving animal health and welfare. On various farms and regions, it has been demonstrated that antibiotic use can be significantly reduced and limited to only what is essential for treating sick animals. AMR monitoring authorities have also noted that a significant reduction in the use of certain antibiotics on farm animals has reversed the trend of rising resistance to these antibiotics. This is promising given the fact that our ultimate objective is to safeguard the efficacy of antibiotics not only in humans, but also in animals. To encourage the rapid adoption of best practices, and in recognition of the importance of nutrition in animal health and welfare, regulatory authorities may have to revise their current legislation on the health claims of feed and feed ingredients. Nutrition can produce significant prophylactic effects, reduce the risk of gastrointestinal diseases and facilitate recovery. This knowledge, which can be used to establish best practices in nutrition, has emerged from strategies to reduce antimicrobial resistance, and now needs to be shared, used and tailored to the conditions on individual farms and countries. In light of new technologies in animal health care, animal health monitoring devices and precision livestock farming, it is likely that we will be able to have a more rapid and effective impact in the future.

TABLE 5
Summary of dietary measures to support gastrointestinal health in weaned piglets.

Topic	Recommended measures
Key feed management practices	Feeding piglets pre-weaning is recommended in order to support the development of the GIT and help them adapt to solid feed post-weaning. Feeding and drinking water systems need to facilitate high feed and water intake in the first 48 hours post-weaning.
Feed form and particle size	Liquid diets lead to the highest intake, but are practically challenging. The use of coarsely milled cereals in feed in order to support the pH barrier function in the stomach and facilitate GIT motility and secretions should be considered. The inclusion of coarse fibre sources is another option. A further alternative is to provide mash to slow down feed intake, although feed spillage may be a problem.
Protein	Reduce crude protein level whilst meeting minimum digestible amino acid levels (crude protein max. 17%–19%). Limit the amount of indigestible protein. The use of highly digestible protein sources is recommended in general.
Amino acids	Increase the ratio of amino acids which have a positive impact on health, e.g. sulphur amino acid, tryptophan and threonine to lysine to 60%–65%, 21%–22% and 70%, respectively (Pluske, Turpin and Kim, 2018).
Starch	Replace fat with starch up to a minimum level (35%). The digestion of starch and uptake of glucose are less disrupted by gastrointestinal disorders.
Sugars	Include minimum amount of lactose in the diets of early-weaned piglets (<4 weeks of age) as a readily digestible energy source and prebiotic. Thereafter, its effect may be limited. The addition of sugars (sucrose) improves palatability.
Fat	Limit use of fat (max 5%) in the first phase post-weaning. Fat digestibility and absorption is compromised in the immediate post-weaning phase, especially if the fat source is highly saturated.
Fibre level and sources	Include insoluble bulking fibre sources to promote GIT secretions and motility.
Calcium	Reduce amount of limestone or other buffering Ca sources to support low pH in stomach. Avoid high calcium levels but meet min. requirements. Calcium salts of organic acids can be used as sources of Ca with a low acid-binding capacity.
Phosphorus	Consider use of phytase to limit use of buffering sources of P and to limit anti-nutritional properties of phytate.
Sodium	Total dietary levels of up to 0.40% sodium can improve palatability and growth performance. Promote feed intake in the first few days post-weaning.
Copper, zinc	Higher levels of copper (150–250 ppm) and zinc oxide (2500–3000 ppm, first two weeks post-weaning only) reduces incidence of diarrhoea. Environmental pollution and risk of co-selection for antimicrobial resistance are public concerns.
Functional macro-ingredients	Option to use plasma protein, milk protein and lactose and/or hyperimmunized egg protein in first-phase diet after weaning.
Feed additives	Use organic acids to acidify the feed and possibly also drinking water. Combining with MCFAs and phytogenics may further enhance antimicrobial activity. Additional options include pre- and probiotics and phytogenics to modulate the intestinal microbiome and support mucosal barrier function. Consider routine use of phytase and NSP-ase to support digestion in post-weaning phase.

TABLE 6
Summary of dietary measures to support gastrointestinal health in broiler chickens.

Topic	Recommended measures
Key feed management practices	Early access to feed and water post-hatch is critical to prevent dehydration and promote the development and functioning of the GIT.
Feed form and particle size	Feed should be pelleted, or pelleted and crumbled, mainly for feed efficiency reasons. Use whole wheat, coarsely milled cereals or coarsely ground insoluble fibre particles is recommended to promote development and functioning of proventriculus and gizzard.
Protein, amino acids	Reduce crude protein levels whilst maintaining minimum digestible amino acid levels. In addition to promoting GIT health, this will also help control litter quality.
Starch and sugars	Replacing fat with a minimum amount of readily digestible carbohydrates will improve performance in challenge conditions.
Fat	Dietary fat should include a minimum amount of unsaturated fatty acids. Unsaturated fatty acids are more readily digestible in challenge conditions than saturated fatty acids. Limit the amount of total fat.
Fibre level and sources	Consider including minimum amount of insoluble fibre. Limit dietary levels of soluble fermentable fibre. NSP-degrading enzymes are strongly recommended, depending on the NSP composition of the diet.
Calcium	Reduce amount of limestone or other buffering calcium sources to support rapid decrease in pH in proventriculus and gizzard. Avoid high calcium levels but cover min. requirements.
Phosphorus	Consider use of phytase to limit use of buffering phosphorus sources and to eliminate anti-nutritional properties of phytate.
Sodium	Increasing sodium levels may increase feed intake but is in general not recommended due to the risk of wet litter.
Copper, zinc	Supra-nutritional copper levels may contribute to controlling microbial activity in the GIT. Environmental pollution and risk AMR are public concerns. High zinc oxide should not be used for toxicity reasons.
Functional macro-ingredients	Functional ingredients such as spray-dried plasma and egg powder may only be economically feasible in (pre-) starter feed.
Feed additives	Use of organic acids to acidify the feed and drinking water is an option during critical phases. Combining organic acids with MCFAs and phytogenics may further enhance antimicrobial activity. Additional options include pre- and probiotics and phytogenics to modulate the intestinal microbiome and support mucosal barrier function. Phytase and NSP-ase to be used as a standard measure.

TABLE 7
Summary of dietary measures to support gastrointestinal health in calves.

Topic	Recommended measures
Key feed management practices	A minimum of four litres of colostrum has to be fed to calves within six hours of birth. Thereafter, calves can be fed whole milk or CMR. Whole milk needs to be pasteurized before feeding. Waste milk which contains antibiotic residues should not be fed to calves. Free access should also be provided to drinking water. Additional access to straw or other roughage is recommended. Transition from milk to solid feed should be carried out gradually.
Protein and amino acids	Skim milk powder or whey powder are recommended as highly digestible protein sources that can be used to limit the amount of indigestible protein. The use of plant proteins may result in higher levels of indigestible protein. Relatively little information is available on the amino acid requirements of calves during GIT health challenges.
Starch and sugars	Lactose is preferred as an energy source. Calves have a relatively low ability to digest starch compared to swine.
Fat	Unsaturated fats are preferred to saturated fats. Emulsification, used to facilitate the preparation of artificial milk from powder, may further support fat digestion.
Fibre level and sources	Some straw and roughage as additional feed is recommended to support development of the GIT tract. CMR (or whole milk) usually contains no or limited fibre sources.
Calcium, phosphorus, sodium	Relatively little information is available on the optimum levels of calcium, phosphorus and sodium to promote gastrointestinal health in calves.
Copper, zinc	The use of high copper or zinc levels is not permitted nor practised in calf nutrition.
Functional macro-ingredients	The use of spray-dried plasma may promote health in calves. However, it may not be permitted for use in calf nutrition due to legal constraints. Egg powder derived from the eggs of hyperimmunized laying hens is a potential alternative.
Feed additives	The use of organic acids to acidify CMR is not common but may be worth considering. Additional options include butyrate, pre- and probiotics and phytogenics to modulate the intestinal microbiome and support mucosal barrier function.

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Glossary

Antibiotic (*noun*): naturally occurring, semi-synthetic or synthetic substances with bacteriocidal (bactericidal) or bacteriostatic properties at concentrations attainable *in vivo*.

Antibiotic (*adj.*): having bacteriocidal (bactericidal) or bacteriostatic properties at concentrations attainable *in vivo*.

Antifungal (*noun*): naturally occurring, semi-synthetic or synthetic substances with fungicidal or fungistatic properties at concentrations attainable *in vivo*.

Antifungal (*adj.*): having fungistatic or fungicidal properties at concentrations attainable *in vivo*.

Antimicrobial[3] **(*noun*):** naturally occurring, semi-synthetic or synthetic substances with microcidal (microbiocidal) or microstatic (microbiostatic) properties when at concentrations attainable *in vivo*.

Antimicrobial (*adj.*): having microcidal (microbiocidal) or microstatic (microbiostatic) properties at concentrations attainable *in vivo*.

Antimicrobial resistance (*noun*): the ability or state of microorganisms to survive and/or proliferate in concentrations of antimicrobials that would otherwise be microbiocidal or microbiostatic to other organisms of the same or similar species.

Antimicrobial-resistant (*adj.*): the phenotypic characteristic of microorganisms to survive and/or proliferate in concentrations of antimicrobials that would otherwise be microbiocidal or microbiostatic to other organisms of the same or similar species.

Antiparasitic (*noun*): naturally occurring, semi-synthetic or synthetic substances that inhibit or kill micro- and macro-parasites at concentrations attainable *in vivo*.

Antiparasitic (*adj.*): having the ability to inhibit or kill parasites at concentrations attainable *in vivo*.

Antiprotozoal (*noun*): naturally occurring, semi-synthetic or synthetic substances that kill or inhibit organisms of the phylum Protozoa at concentrations attainable *in vivo*.

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[3] Example exclusions: anti-helmintics, disinfectants, antiseptics. Example inclusions: bacteriophages, anti-protozoal agents (e.g. coccidiostats, anti-malarials, drugs for *Toxoplasma* spp. and *Babesia* spp., etc.), and metals used *in vivo* or *in planta*.

Antiprotozoal (*adj.*): having the ability to inhibit or kill organisms of the phylum Protozoa.

Antiviral (*noun*): naturally occurring, semi-synthetic or synthetic substances with virostatic activity.

Antiviral (*adj.*): having virostatic properties.

Bacteriocidal (*adj.*): having the ability to destroy or inactivate organisms of the kingdoms Archeabacteria and Eubacteria.

Bacteriostatic (*adj.*): having the ability to inhibit the reproduction or replication of organisms of the kingdoms Archeabacteria and Eubacteria.

Feed (*noun*): Any single or multiple materials, whether processed, semi-processed or raw, intended to be fed directly to food-producing animals.

Feed additive (*noun*): Any intentionally added ingredient not normally consumed as feed by itself, whether or not it has nutritional value, which affects the characteristics of feed or animal products. Microorganisms, enzymes, acidity regulators, trace elements, vitamins and other products are covered by this definition, depending on the purpose of use and method of administration.

Fungistatic (*adj.*): having the ability to inhibit the reproduction or replication of organisms of the kingdom Fungi.

Fungicidal (*adj.*): having the ability to destroy or inactivate organisms of the kingdom Fungi.

Microorganism (*noun*): viruses and unicellular species of the kingdoms Archaebacteria, Chromista, Eubacteria, Protista and Fungi.

Microstatic/microbiostatic (*adj.*): having the ability to inhibit the reproduction or replication of microorganisms.

Microcidal/microbiocidal (*adj.*): having the ability to destroy or inactivate microorganisms.

Parasite (*noun*): an organism whose survival is dependent upon living on or in a host organism and which feed from or at the expense of its host.

Parasitic (*adj.*): pertaining to or having the characteristics of a parasite.

Virostatic (*adj.*): having the ability to inhibit the replication of viruses.

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Antimicrobial resistance is a global and increasing threat. Stewardship campaigns have been established, and policies implemented, to safeguard the appropriate use of antimicrobials in humans, animals and plants. Restrictions on their use in animal production are on the agenda worldwide. Producers are investing in measures, involving biosecurity, genetics, health care, farm management, animal welfare and nutrition, to prevent diseases and minimize the use of antimicrobials. Functional animal nutrition to promote animal health is one of the tools available to decrease the need for antimicrobials in animal production. Nutrition affects the critical functions required for host defence and disease resistance. Animal nutrition strategies should therefore aim to support these host defence systems and reduce the risk of the presence in feed and water of potentially harmful substances, such as mycotoxins, anti-nutritional factors and pathogenic bacteria and other microbes. General dietary measures to promote gastrointestinal tract health include the selective use of a combination of feed additives and feed ingredients to stabilize the intestinal microbiota and support mucosal barrier function. This knowledge, used to establish best practices in animal nutrition, could allow the adoption of strategies to reduce the need for antimicrobials and, in turn, contribute to contain antimicrobial resistance.

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