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Review article

Role of vitamins for gastro-intestinal functionality and health of pigs

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ABSTRACT

Several nutritional studies have been performed to improve piglet health and resilience to infectious diseases during the lactation and post-weaning periods, and to identify alternatives to the use of antibiotics and antimicrobials as growth promoters. In the last decades, pharmacological levels of zinc oxide (ZnO) and copper have frequently been used as nutritional strategies to prevent post-weaning diarrhoea because of their antimicrobial activity. However, the use of ZnO was recently banned by the EU from 2022 because of the risk of promoting Anti-Microbial Resistance (AMR). Beyond their role as essential micronutrients, vitamins share several remarkable activities (antimicrobial, immunological and antioxidative) often referred to amongst many of the non-antibiotic feed additives commonly proposed and used for pigs. However, very little research and scientific emphasis are devoted to vitamin nutrition and its role in the gut function and health of livestock. This review discusses how fat-soluble (A, D, E and K) and water-soluble (B-group and C) vitamins may influence gastrointestinal (GI) functionality in general and with specific importance on the challenges associated with the early life of pig gut health and disease prevention. On the basis of the literature review it is suggested that future research and development of alternative strategies to antibiotics and medicinal ZnO should pay attention to the role of vitamins for GI functionality and health of pigs.

1. Introduction

Much recent research and commercial interests in pig nutrition have focused on gastrointestinal (GI) functionality, optimal immune function and regulation of microbiota, with special emphasis on the period following weaning of the piglet from the dam. During this

Abbreviations: AMR, Anti-Microbial Resistance; ARA, arachidonic acid; ChAT, choline acetyltransferase CON A Concavalin A; DC, dendridic cells; ETEC, Entero Toxigenic *Escherichia coli*; GALT, Gut-Associated Lymphoid Tissues; GI, Gastrointestinal; GIT, GI tract; GSH-Px, gluthathione peroxidase; Hcy, homocysteine; IBD, inflammatory bowel disease; Ig, immunoglobulin; IL, interleukin; LPS, lipopolysaccharide; PGE2, prostaglandin E_2; PLA_2, phospholipase A_2; PWD, post-weaning diarrhoea; NADPH, nicotinamide adenine dinucleotide phosphate; NOS, nitric synthase; RNS, reactive nitrogen species; ROS, reactive oxygen species TNF-α tumor necrosis factor-alpha; ZnO, zinc oxide; TJ, tight junction; VDR, vitamin D receptor; ZO, zona occludens.

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Table 1
Potential vitamin B-producing bacteria and implication in the porcine intestine (adapted from Magnúsdóttir et al., 2015; Yoshii et al., 2019 and Looft et al., 2014).

Vitamin	Vitamin B family-producing bacteria	Absent or very rare bacterial genomes for biosynthesis	Presence (%) of human gut microbial genomes for vitamin B biosynthesis	Implication for the porcine gut (presence of major bacterial communities)
Thiamin	*Bacteroides fraglis, Prevotella copri* *Lactobacillus* (plantarum, curvatus, lactaris), *Clostridium difficile* *Ruminocuccus lactaris, Bifidobacterium* (infantis, bifidum), Fusobacterium	Prevotella salivae DSM 15,606	56%	Bacteroides highly represented in caecum, colon and faeces (not in ileum) Lactobacillus in ileum Clostridium difficile in ileum Ruminocuccus in ileum Some firmicutes in caecum and colon Prevotella highly represented in caecum and colon
Riboflavin	*Bacteroides fraglis, Prevotella copri* *Lactobacillus (plantarum, fermentum), Clostridium difficile* *Ruminocuccus lactaris, Bifidobacterium* (infantis), *Helicobacter pylori* *Fusobacterium varium*	Actinobacteria	65 %	Bacteroides highly represented in caecum, colon and faeces (not in ileum) Lactobacillus in ileum *Clostridium difficile* in ileum Ruminocuccus in ileum Some firmicutes in caecum and colon Helicobacter Pylori[1]
Niacin	*Bacteroides fraglis, Prevotella copri* Clostridium difficile *Bifidobacterium* (infantis), *Helicobacter pylori* *Fusobacterium varium*	Actinobacteria, Firmicutes	63 %	Bacteroides highly represented in caecum, colon and faeces (not in ileum) Lactobacillus in ileum Clostridium difficile in ileum Ruminocuccus in ileum Some firmicutes in caecum and colon Helicobacter Pylori[1]
Pantothenic acid	Nearly all genomes (Magnúsdóttir et al., 2015). *Bacteroides fraglis, Prevotella copri* *Bifidobacterium (longum)* *Collinsella aerofaciens,* *Helicobacter pylori* (Yoshii et al., 2019)	Fusobacteria, certain Actinobacteria, Firmicutes	51 %	Bacteroides highly represented in caecum, colon and faeces (not in ileum) Lactobacillus in ileum Clostridium difficile in ileum Ruminocuccus in ileum Some firmicutes in caecum and colon Helicobacter Pylori[1]
Vitamin B-6	Majority of the *Actinobacteria, Bacteroidetes* and Proteobacteria (Magnúsdóttir et al., 2015). *Bacteroides fraglis, Prevotella copri* *Bifidobacterium* (longum) *Collinsella aerofaciens*, *Helicobacter pylori* (Yoshii et al., 2019)	Firmicutes and Fusobacteria	50 %	Some firmicutes in caecum and colon Bacteroides highly represented in caecum, colon and faeces (not in ileum) Proteobacteria in ileum Some firmicutes in caecum and colon
Biotin	*Bacteroides fraglis*, *Lactobacillus helveticus* *Fusobacterium varium, Camphylobacter coli*	Actinobacteria, Firmicutes	40 %	Bacteroides highly represented in caecum, colon and faeces (not in ileum) Lactobacillus in ileum Some firmicutes in caecum and colon
Folates	Nearly all Bactereoides, Fusobacteria, Proteobacteria (Magnúsdóttir et al., 2015).	Actinobacteria, Firmicutes	43 %	Bacteroides highly represented in caecum, colon and faeces (not in ileum) Lactobacillus in ileum Some firmicutes in caecum and colon
Vitamin B-12	Half of the Bacteroides and Firmicutes (Magnúsdóttir et al., 2015).	Lactobacillales	42 %	Bacteroides highly represented in caecum, colon and faeces (not in ileum)

(*continued on next page*)

Table 1 (*continued*)

Vitamin	Vitamin B family-producing bacteria	Absent or very rare bacterial genomes for biosynthesis	Presence (%) of human gut microbial genomes for vitamin B biosynthesis	Implication for the porcine gut (presence of major bacterial communities)
				Lactobacillus in ileum Some firmicutes in caecum and colon

[1] *Helicobacter Pylori*: Information obtained from Yoshii et al., 2019. In pigs, the *Helicobacter Suis* would be the relevant proteobacteria in the stomach.

period, one of the most frequent production diseases is related to post-weaning diarrhoea (PWD) primarily caused by enteric infection by enterotoxigenic *Escherichia coli* (ETEC) (Fairbrother et al., 2005). PWD is a major challenge for the pig farmer due to its economic and welfare impact, and for the society as it promotes the use of antibiotics and heavy metals such as medical Zinc Oxide (ZnO**)** with the consequent risk of developing bacterial Anti-Microbial Resistance (AMR) (WHO, 2012). While many nutrients and feed additives have been suggested to possess immunomodulatory and antimicrobial properties (Liu et al., 2016; Markowiak and Śliżewska, 2018; Roselli et al., 2005 2017; de Lange et al., 2010), very little emphasis has been dedicated to vitamins although these micronutrients are well-known for their bioactivity and role in relation to health and immune function in human (Yoshii et al., 2019; Kau et al., 2011; Wintergerst et al., 2007) and animals (Lee and Han, 2018; Smith et al., 2018), including inflammatory disease processes of the GI tract (GIT) (Suzuki and Kunisawa, 2015; Calder et al., 2009). Vitamin deficiency is linked to increased susceptibility of enteric infectious diseases (De Santis et al., 2015), and although deficiency of vitamins does not seem to appear in conventional swine-production systems, it should be noted that requirements of vitamins by modern highly producing genotypes may be higher than previously estimated (Matte and Lauridsen, 2013; Lauridsen and Matte, 2017). However, the definition of gut health does not only encompass pathogens causing illness, mortality and morbidity to pigs, but also the function of the GIT in which the key components are diet, effective structure of the GI barrier, host interaction with the GI microbiota, effective digestion and absorption of feed, and effective maturation and development of innate and acquired immune functions (Celi et al., 2017). In addition, the enteric nervous system (ENS) and its association with the endocrine system and the parasymphatic nervous system plays a key role for the structure and function of the GIT and the health and well-being of the animal (Moeser et al., 2017; Pluske et al., 2018). With these definitions, the purpose of this review is to provide an overview of the mode of action of the vitamins in relation to the GIT functionality of pigs as well as discussing how dietary vitamins and vitamin status of the animal impact the gut microbial ecology, host physiology and health.

2. Microbiota and vitamins

The pig GIT harbours 500–1000 bacterial species that play important roles in health and disease of the host. Usually, the host and the gut microbiota live in a commensal manner. The early-life transfer of microbiota from the sow to the piglet through the birth channel and colostrum and milk has a major impact on the colonisation of the microbes and the successive microbial diversity and immune processes in the piglets (Schokker et al., 2014; Poulsen et al., 2018). Subsequently, the weaning of piglets from the sow, and especially the change in diet from liquid (milk) to solid feed, has a dramatic effect on the intestinal microbiota (Moeser et al., 2017). While nursing piglets are dominated by *Enterobacteriaceae*, *Bacteroidaceae* and *Clostridiaceae*, these bacterial families may significantly decrease after weaning when compared to other bacterial populations (Poulsen et al., 2018). Further, when the diet is characterised by plant- or animal-based components rather than sow milk, the piglets' intestinal microbiota diversity increases, and piglets' intestine is dominated by *Prevotellaceae* and *Ruminococcaceae. Lactobacillaceae* is a stable and important coloniser of the small intestine of pigs, and its relative abundance increases in piglets post weaning (Guevarra et al., 2018). After weaning, stress caused by change of feed and environmental conditions induces intestinal dysbiosis and activation of intestinal defences (Gresse et al., 2017). These conditions predispose the entire intestinal function to deal with burdens during the transition period and therefore may influence bacterial synthesis and host requirement of vitamins.

2.1. Synthesis and utilisation of vitamins

It is well-known that the gut microbiota synthesises not only B-vitamins like biotin, vitamin B-12, folates, niacin, pantothenic acid, vitamin B-6, riboflavin and thiamin but also vitamin K (Hill, 1997). Not only are these vitamins involved in the bacterial metabolism, as also demonstrated in a recent study in C. elegans (Maynard and Weinkove, 2020), but they can also influence host metabolism and physiological responses. Regarding B-vitamins (Table 1), *Bacteroidetes* appears to be the phylum with the greatest number of vitamin B producers (more than 90 %) excluding vitamin B-12 (Rowland et al., 2018), and this is also the major bacterial community in the colon of the pig (Looft et al., 2014). Interestingly, Magnúsdóttir et al. (2015) identified several groups of bacterial organisms in the human gut whose B-vitamin synthesis pathway patterns complemented each other thus implying co-operation between gut microbes. Genomic assessment suggested that the major proportion of microbial-synthesised B-vitamins is utilised by other non-vitamin-producing bacteria hence reducing the availability of these vitamins for the host (Table 1). This was also stated in the review by Yoshii et al. (2019), indicating that the composition and function of the microbiota affect the host microbiota usage of B-vitamins having extended effects on enteric immune function. Hence, although it is generally considered that the colon microbiota produces vitamins K and B, it is not often thought through that the major site of vitamin absorption is the ileum, and that vitamins are

also used up by other microbes, meaning that less would be available for the host. For example, *Faecalibacterium spp*. (Firmicutes) must obtain their thiamin from other bacteria or from the host diet, suggesting that there is competition for thiamin between the host and certain intestinal bacteria (Yoshii et al., 2019). This bacterium was, however, not mentioned in the swine intestinal bacterial communities (Looft et al., 2014), and in general the vitamin-using bacteria seem to be less represented in the pig gut (Table 1). Further, it has been assumed for several decades that the microbiota can significantly contribute to vitamin intake in pigs through coprophagy (ARC, 1981; McDowell, 2001) since several B-complex vitamins are synthesised in the caecum and large intestine by bacterial microflora and excreted in the faeces. However, under current conventional livestock housing conditions, the coprophagy behaviour is negligible (de Passillé et al., 1989) and cannot provide a reliable supply of B-complex vitamins, at least for folic acid, vitamin B-12 and biotin (Bilodeau et al., 1989). Moreover, the widespread use of slatted floors in pig barns can only further marginalise the importance of coprophagy as a source of B-complex vitamins in swine. In other housing systems such as organic or outdoor housing systems, coprophagy may be more frequent. Mulder et al. (2009) investigated microbial changes in outdoor- and indoor-housed pigs and found that pigs housed in natural outdoor environments had a higher dominance of Firmicutes, mainly *Lactobacillus*, whereas pigs housed indoor in hygienic compartments had a lower number of *Lactobacillus* and a higher number of potential pathogenic phylotypes. Hence, housing systems may influence the composition of the microflora of pigs and hence bacterial synthesis and usage of vitamins in the pig.

Little is known both in pigs and humans regarding the impact of changes in the microbiota with regard to vitamin synthesis, including how bioavailability of individual vitamin forms may be influenced by microbial changes along both the small and large intestinal tract. It has been long believed that vitamin absorption occurs only in the small intestine (Le Grusse and Watier, 1993; McDowell, 2001; Combs and McClung, 2017), but recent evidence in human and rodent models strongly suggests that it may also take place in the large intestine (colon) for several B-vitamins (Said and Nexo, 2018; Yoshii et al., 2019). Efficient and specialised carrier-mediated systems for the absorption of bacterial-synthesised B-vitamins have been identified (thiamin, folates, biotin, riboflavin, pantothenic acid) as described by Said and Nexo (2018) and Yoshii et al. (2019). Therefore, part of the colonic-synthesised vitamins could play a role in the fine tuning of the normal body homeostasis of these vitamins (Magnúsdóttir et al., 2015).

Riboflavin and vitamins B-6 and B-12 are involved in both folates metabolism and one-carbon metabolism. Deficiency or suboptimal levels of these vitamins have been linked to the risk of developing a number of human infectious, inflammatory and allergic diseases (Yoshii et al., 2019). As described by Said and Nexus (2018) and Yoshii et al. (2019), this is via the composition and function of the microbiota affecting the B-vitamins' usage with extension to host immunity, and, according to Bhat and Kapila (2017), via the modulation of the host genetics and even epigenetic modifications. Hence, it is expected that also the composition of the porcine enteric microbiota and changes of the microbiome may influence the synthesis of vitamin K and the B-vitamins, which can directly or indirectly cause epigenetic changes in the host and influence the GI functionality.

2.2. Impact of antibiotics on vitamins' synthesis by microbiota

The use of an antibiotic treatment suppresses the microbiota and changes its composition, and, as shown in pigs, medication increases the abundance and diversity of antibiotic resistent genes (Adhikari et al., 2019). Although scanty data are available in pigs (Janczyk et al., 2007; Poulsen et al., 2018), there is instead strong evidence in human that the disruption of the commensal with oral antibiotics often precedes the emergence of several enteric pathogens (Amadori and Zanotti, 2016). It is known that subtherapeutic levels of antibiotics in broilers can influence the digestion and absorption of fat and hence of fat-soluble vitamin E (Knarreborg et al., 2004), and something similar can happen to the other fat-soluble vitamins A, D and K. The mechanism behind these results could probably be ascribed to the fact that the microbiota composition influences microbial deconjugation of bile salts, and this can be modulated by the use of antibiotics. A number of gut bacteria, such as *Bacteroides, Bifidobacterium, Clostridium* and *Lactobacillus*, possess bile salt hydrolase enzymes that can hydrolyze both glycol and tauro-conjugates. The bacterial deconjugation reduces the efficacy of bile acids for the emulsification of dietary lipid and micelle formation. Thereby bacterial composition can modify the digestion of the lipid-soluble vitamins. In addition, bile-salt dependent enzymes, such as carboxylic ester hydrolase, influence the hydrolysis of vitamin esters (retinyl palmitate and tocopheryl acetate) as shown *in vitro* by Lauridsen et al. (2001). Hence, antibiotic treatment may lead to changes in the GIT commensal microbial populations, which may influence both vitamin synthesis (in the small intestine and the colon) and absorption (in both small intestine and colon). In an *in vivo* experiment with post-weaned piglets, it was recently observed that a diet supplemented with an antibiotic (chlortetracycline) increased blood plasma concentrations of pyridoxine by 66 % compared to the corresponding antibiotic-free diet (unpublished data, personal communication Martin Lessard), whereas no dietary treatment effect was observed for folates, vitamin E or vitamin B-12. Such response suggests that chlortetracycline perturbed the intestinal microbiota, likely in favour of bacteria-producing vitamin B-6, and this has apparently occurred as early as at the level of medial (jejunum) small intestine where most of this vitamin is absorbed (McDowell, 2001; Le Grusse and Watier, 1993). The phenomenon needs to be better understood, possibly in relation with changes in partition of bacterial populations using and/or producing vitamins. As it has a potential to influence systemic vitamin status in these young animals, further studies deserve to include all vitamins.

2.3. Impact of vitamins and dietary factors on intestinal microbiome

Dietary vitamin supplementation may not only influence the composition but also the activity of bacterial communities in the gut, and recent research has shown that vitamins may play important roles in bacterial metabolism and gene regulation (Degnan et al., 2014). Degnan et al. (2014) discussed specifically how vitamin B-12 impacts diverse host-microbiome symbiosis in humans and that this vitamin may make an unrecognised contribution in shaping the structure and function of human gut microbial communities. Such eubiotic activities of vitamin B-12 may also be expected in pigs, and other vitamins may influence gut microbial populations through

their recognised antimicrobial or even antimicrobicidal activities as discussed recently for vitamin C in relation to human bacterial infections (Mousavi et al., 2019). Similar properties might be crucial in the context of the current pressure for short-term husbandry solutions to mitigate the dissemination of antimicrobial resistance in bacterial pathogens. Luo et al. (2013) showed that broilers fed dietary vitamins at NRC levels harboured higher diversity of the caecal bacteria and higher proportions of *Clostridium*, *Faecalibacterium* and *Lactobacillus* than broilers fed no dietary vitamins, suggesting that lack of dietary vitamins can increase the ratio of facultative pathogenic bacteria and decrease the diversity of bacteria in the caecum of broilers. Interestingly, a recent study demonstrated synergistic actions of vitamins (A, B_1, B_2, B_6, B_{12}, C, D, E and K) with antibiotics against bacterial strains (Shahzad et al., 2018). The effect varied between the different vitamins and among the Gram-positive and Gram-negative bacterial strains with riboflavin being the most effective in synergism with antibiotics against the methicillin-resistant *Staphylococcus aureus* (MRSA), which is of special concern for pig production. More research is required to study the mechanisms of interactions between antibiotics and vitamins as well as their interactions with bacterial cells and network within the GIT.

The gut microbiota can be modulated by several dietary factors, which can be both harmful and beneficial for the microbiome. Undigested substrates mainly determined by the nutrient composition and feed intake flow from the small into the large intestine. While undigested carbohydrates that flow into the hindgut is associated with beneficial effects, excessive protein fermentation by the microbiota in the hindgut can cause intestinal dysbiosis, resulting in inflammatory bowel disease (IBD) in human and post-weaning diarrhoea (PWD) in pigs (Gilbert et al., 2018). Bile acids, which are important microbiota modulators, may (if non-absorbed) favour the growth of bile-acid tolerant bacteria (Gilbert et al., 2018). Besides considering all non-digestible carbohydrates as 'true' prebiotics, it is now recognised that several non-carbohydrate structures, such as polyphenols, minerals or vitamins, can also exert this function. Khan et al. (2012) suggested that vitamin B_2 can affect the growth of the anaerobic bacteria *Faecalibacterium prausnitzii*, a producer of butyrate possessing anti-inflammatory properties. Anaerobic bacteria have no direct enzymatic means (e.g. catalase and peroxidase) to protect themselves from oxygen and reactive oxygen species (**ROS**). Riboflavin, acting as redox mediator, can reduce the oxygenated environment using their metabolism and thus reducing oxidative stress. Steinert et al. (2016) administered 100 mg of riboflavin per day for 14 days to a group of volunteers and found that the number of *Faecalibacterium prausnitzii* per gram of faeces increased during supplementation, and their number dropped again, although not to the baseline levels, after a 1-week washout period. An increase in *Roseburia* species, another anaerobe, and a decrease in *E. coli* were also noticed in this study (Steinert et al., 2016). It is worth mentioning that IBD, and especially Crohn's disease, is characterised by low levels of *Faecalibacterium prausnitzii* and an increased number of *E. coli* (Willing et al., 2009). During an imbalance of the intestinal microbiota or during dysbiosis, the synthesis and usage of B-vitamins in the colon can also be impaired. With regard to vitamin D, a recent review based on mice and small human populations supported the hypothesis that vitamin D influences the composition of the gastrointestinal microbiome (Waterhouse et al.,

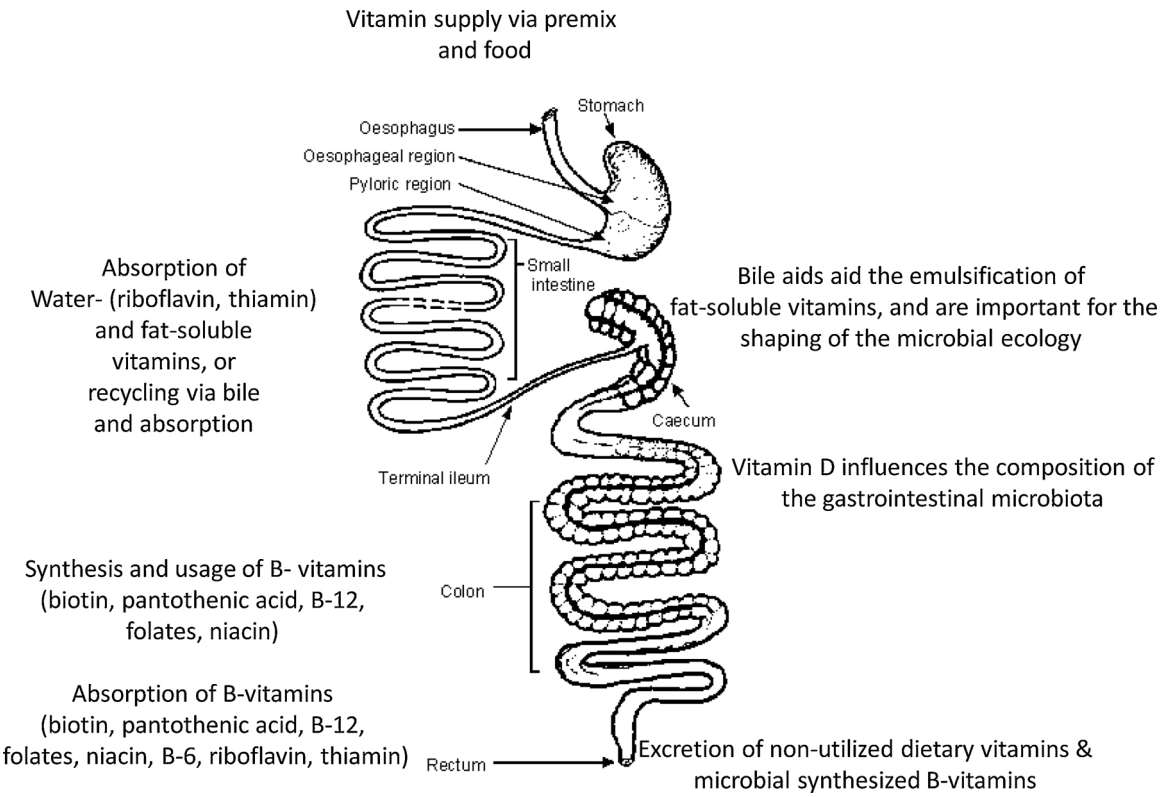

Fig. 1. Summary of the major interactions between vitamins and microbiota in the GIT.

2019), and, in humans, supplementation with vitamin D modulated the gut microbiota composition in the upper GIT, such as lower relative abundance of Gammaproteobacteria including *Pseudomonas* spp. and *Escherichia/Shigella* spp., and higher bacterial richness (Bashir et al., 2016). A recent study in pigs showed that maternal $25OHD_3$ affected bacterial metabolites in the hindgut of the suckling piglets (Zhang et al., 2019). Further, vitamin D deficiency resulted in an altered faecal microbiota composition in both an absence and a presence of an infectious challenge of mice (Assa et al., 2014). The mechanisms by which vitamin D regulates the gut microbiota involve the roles of host-expressed vitamin D receptors (**VDR)** in maintaining the integrity of intestinal barrier and controlling mucosal inflammation (Li et al., 2015). In fact, $125(OH)_2D_3$ deficiency or lack of VDR could lead to dysbiosis of gut microbiota and is more likely to induce intestinal diseases (Ooi et al., 2012 2013). Likewise, vitamin A exposes important regulatory activities of the gastrointestinal microbiota via vitamin A receptors, and changes in vitamin A status, and even transient changes, can result in dysbiosis of the microbial communities in the gut (Cantorna et al., 2018).

The major interactions between vitamins and microbiota in the GIT are summarised in Fig. 1.

3. Mechanisms by which vitamins can influence the host immune function

Excellent descriptions of the intestinal immune system of pigs are available (such as Bailey et al., 2013). Although the defence mechanisms provided by the innate and adaptive immune functions are very complex they can be described as being organised in three clusters: 1) physical barriers (e.g. mucosa, mucus secretions, epithelium, tight junction proteins), 2) cells involved in mucosal defence, such as epithelial cells, natural killer cells, dendritic cells (DC), macrophages, natural killer cells, gamma-delta T cells and B lymphocytes, Paneth cells and 3) production of antibodies, antimicrobial peptides (AMP) and other molecules limiting pathogens to grow and to invade the host. In general, deficiency of micronutrients suppresses immunity by affecting both innate and adaptive immune responses, leading to dysregulation of the balanced host response. In addition, it is well-known from other animal species, including human, that an adequate intake of vitamins and other micronutrients is required for the immune system to function efficiently, and clinical evidence has long indicated that inadequate intake of vitamins disrupts host immunity thus predisposing human to infectious and inflammatory diseases (Kunisawa and Kiyono, 2013; Wintergerst et al., 2007). Epidemiologic evidence supports the hypothesis that a low serum $25OHD_3$ concentration can be considered as an environmental factor involved in IBD, Crohn's disease and ulcerative colitis risk (Meckel et al., 2016). Yoshii et al. (2019) reviewed the immunological functions of B-vitamins and concluded that B-vitamin-mediated immunological regulation is specific to diff ;erent immune cells and immune responses: that is, diff ;erent B-vitamins are required for developing various types of immune responses. Vitamin C does not only impact immune cell functionalities but also immune cell development as recently reviewed in relation to human (Mousavi et al., 2019), who, contrary to swine, has lost their vitamin C-synthesising capacities during evolution. The role of vitamin E in modulation of immune responses in humans and the effects of vitamin E supplementation in relation to infectious diseases were reviewed, showing cell-specific effect of vitamin E (Lee and Han, 2018). Hence, it seems well-established that vitamins have an important immunomodulatory impact in human and that vitamin status is an important factor contributing to immune-competence in humans (Morse and High, 2014) and, to some extent, animals (Smith et al., 2018). However, much less is known regarding the role of vitamins for immune function in livestock (Smith et al., 2018), and especially in pigs, including relationship to gut immunity and specifically immune cell functions. We will here highlight the importance of the vitamins for the key immune functions with focus on the GI functionality.

3.1. Mucosal immunity

Vitamins A and D share several of the mechanisms by which they can regulate intestinal immune functions, and one of the key elements is the fact that epithelial cells and immune cells express the vitamin A receptor (retinoic acid receptor, RAR) and the VDR. Moreover, vitamins A and D can modulate the intestinal barrier function, the production of AMP and mucosal immune responses such as effects on regulatory T-cells in the gut (Cantorna et al., 2018). The vitamin B-complex, vitamin C and vitamin E have effects on distinct immune cell populations and their functions. A brief overview on each vitamin and the role for immune regulation are given below.

Vitamin A: The importance of vitamin A in the regulation of intestinal immunity has long been indicated, and, generally speaking, vitamin A is important for fundamental immunological functions, including modulation, differentiation, maturation, migration or activation of DC, T cells and NK cells (Raverdeau and Mills, 2014; Larange and Cheroutre, 2016). Epithelial cells and DC in the intestine uniquely express RALDH and are therefore capable of synthesising retinoic acid (RA). The metabolites of vitamin A (all-trans retinoic acid, 9-cis retinoic acid or other metabolites and nuclear RA receptors) play an important role in the regulation of innate and cell-mediated immunity and humoral antibody response (Erkelens and Mebius, 2017; Larange and Cheroutre, 2016). A key discovery was the role of RA in regulation of cell trafficking by inducing the expression of the gut-homing molecules on activated lymphocytes by intestinal DCs and epithelial cells, which allows them to return to the intestinal compartment (Kunisawa and Kiyono, 2013). Hence, RA plays an important role in determining not only the gut tropism of lymphocytes activated in the intestine but also their differentiation (DC, B- and T-cells). The ability by various cell types in the intestine to sense RA is dependent on their capability to express receptors, which can broadly be classified as two sub-groups: retinoid acid receptor and retinoic X receptor. Studies performed with vitamin A deficient mice have revealed the importance of RA in the mucosal immune system, especially the regulation of cell trafficking into the intestine. Depletion of the RA receptors on B-cells rendered mice with an intestinal microbiota dysfunction and lack of development of adequate immune response after oral immunisation (Pantazi et al., 2015). Furthermore, the differentiation of DC is RA dependent, i.e., bone marrow resident DC have the potential to differentiate to pre-mucosal DC, characterised by the expression of gut-homing receptors, which can give rise to intestinal 103^{+}DC (a subset of DC playing a major role in regulating mucosal immunity), and this step is

in fact enhanced by RA (Czarnevski et al., 2017). Likewise, the RA is necessary to induce the gut-homing receptors on T-cells, and overall it seems that RA plays an essential role in modulating intestinal innate immunity and in the establishment of oral immunological tolerance (Czarnevski et al., 2017; Erkelens and Mebius, 2017).

Vitamin D: The immunomodulatory role of vitamin D_3 or more specifically of the vitamin D metabolites has been increasingly recognised, and an overview of vitamin D_3 biosynthesis, metabolism, transport to target sites with binding to the vitamin D receptor (VDR), and transcription-related effects, including effects on various immune cells, has been presented by Sadarangani et al. (2016). In brief, dietary vitamin D_3 and $25OHD_3$ are metabolised to the active form, $125(OH)_2D_3$, which exerts its biological activities through binding to the VDR, forming a heterodimer with retinoid X receptors to regulate the expression of a large group of genes (Dimitrov and White, 2017). Both VDR and $25OHD_3$ 1-α-hydroxylase (CYP27B1) are expressed in several types of immune cells and are thus able to synthesise $125(OH)_2D_3$ that modulates both the innate and adaptive immune system. These effects may be mediated not only via endocrine mechanism of circulating calcitriol but also via paracrine (cell-cell communication) and intracrine mechanisms (Szymczak and Pawliczak, 2016; O'Brien and Jackson, 2012), which enhances gene expression mediated by vitamin D and the VDR axis. The VDR-mediated genes include the antimicrobial peptides cathelicidin and β-defensin, and $125(OH)_2D_3$ can induce the production of these antimicrobial molecules by epithelial cells and Paneth cells (Kunisawa and Kiyono, 2013). These authors pointed out that the diverse immunological functions of vitamin D contribute to the creation of the first line of defence against pathogens without the induction of aberrant inflammatory responses. The activity of $125(OH)_2D_3$ has been revealed through various molecular and cellular mechanisms, and this bioactive form ($125(OH)_2D_3$), which is metabolite from $25OHD_3$, is capable of promoting macrophage activation and phagocytosis. In a weanling pig model supplemented with vitamin D_3 or its metabolite $25OHD_3$, Konowalchuk et al. (2013) found that leukocyte cell numbers increased, reflecting parallel increase in serum $25OHD_3$ achieved by feeding the metabolite, and overall the study highlighted the potential impact of vitamin D on systemic and mucosal antimicrobial responses (Konowalchuk et al., 2013). Morris et al. (2015) studied the effects of a $25OHD_3$ treatment in layer hens during a mixed coccidia challenge, and challenged layers receiving 100 μg/kg $25OHD_3$ showed a loss in body weight of only 4% compared to a loss in bodyweight of 15 % when $25OHD_3$ was fed at lower doses (Morris et al., 2015). At day 6 post-coccidia challenge, birds with the same treatment had a 3.5-fold increase in interleukin (IL)-10 mRNA amounts in the caecal tonsils and 17 % more CD4+CD25+ cells at 15 days post-coccidia challenge. The authors concluded that supplementing layer birds with the greater amount of $25OHD_3$ showed to be a strategy to direct the immune response towards an anti-inflammatory nature. In another study, Morris and Selvaraj (2014), working on chicken monocytes and a chicken macrophage cell line (HD11), a $25(OH)D_3$ treatment increased the nitrite production and mRNA amounts of IL-1β, IL-10, 1α-hydroxylase and 24-hydroxylase in HD11 cells following LPS stimulation.

B-vitamins: B-vitamins are involved in various pathways of the cell metabolism and have via their role an indirect influence on immunity (Yoshii et al., 2019). For example, vitamins B-6 and folates are essential for metabolism of nucleic acids, amino acids and lipids, and influence cell growth, and deficiency of these vitamins leads to various impairments in the immune responses. In fact, for folic acid in particular, its role is instrumental for metabolism as it is required for synthesis and methylation of DNA, the latter with potential targets for 1.2 million sites within the genome (Smith et al., 2018). In deficiency models, lack of vitamin B-6 leads to lymphoid atrophy and reduced numbers of lymphocytes (Meydani et al., 1995), whereas for folic acid, activities of CD8 + T cells and NK cells are inhibited. The few reports available in swine on the role of B-vitamins on immunity are related to young animals and development of their immune competence. In a study using a 2 × 2 factorial design with vitamin B-6 and tryptophan (Matte et al., 2011), no interaction was found between treatments, but separate responses were observed on antibody response to ovalbumin for tryptophan and on lymphocyte proliferative response to Concavalin A (Con A) and partition of B lymphocyte population for vitamin B_6. It appeared that each nutrient modulates the immune response through independent mechanisms. The tryptophan response was attributed to its effect on niacin (vitamin B_3), which is synthesised in large amounts from dietary tryptophan. Niacin metabolites are recognised to play important roles in regulations of functional properties of different populations of leukocytes involved in innate and adaptive immunity (Matte et al., 2011). The separate response to vitamin B-6 fortification was associated to its co-enzymatic role in the B_6-dependent transulfuration pathway in which the intermediary amino acid homocysteine (Hcy), generated from the methionine cycle, is directed towards cysteine and, eventually, the glutathione peroxidase system (Matte et al., 2011). Hcy is a powerful pro-oxidant with deleterious effects on physiological and immune functions, and high levels may be detrimental for lymphocyte proliferative response and may partially inhibit apoptosis in T lymphocytes (Zhang et al., 2002). In suckling pigs, there is a rapid post-natal increase of homocysteinemia; a condition persisting during the post-weaning period (Simard et al., 2007) and exacerbated by inadequate provision of vitamin B-6 (Zhang et al., 2009). It is noteworthy to mention that the above-mentioned antibiotic (chlortetracycline) administration, which increased blood plasma concentrations of pyridoxine by 66 % compared to the corresponding antibiotic-free diet (Verso. et al., 2020, in press), was also followed by a 40-% decrease of homocysteinemia during the same period. Besides transulfuration, a major metabolic route for disposal of Hcy is re-methylation via the methionine cycle, in which B-12-dependent methionine synthase transfers a methyl group from 5-methyltetrahydrofolate for regeneration of methionine (Bässler, 1997). A recent review in human described a potential antioxidant role of vitamin B-12 to reduce homocysteine-induced oxidative stress (Van de Lagemaat et al., 2019). In pigs, plasma Hcy responds to folic acid and/or vitamin B-12 supplements, but minimum values remain high ((>15 μM) compared with those of other species <10 μM) Simard et al., 2007; Giguère et al., 2008)). In order to assess if such high homocysteinemia is harmful for piglets, an experiment was designed (Audet et al., 2015) using two populations of piglets (birth to 8 weeks of age) with high or low homocysteinemia. These distinct groups were generated by altering the dietary provision of folates and B-12 to sows during gestation and lactation and by direct intramuscular injections of vitamin B-12 to piglets during the suckling period. Detrimental effects were seen again on lymphocyte proliferative response to mitogen activation as indicator of cell mediated immunity. Paradoxically, plasma Hcy was positively correlated with growth rate and feed conversion (gain:feed) in these piglets. Therefore, the only logical interpretation to such results would be that young "high-performing" piglets which also generate

high levels of plasma Hcy appear to be immunologically suppressed (Audet et al., 2015) and, speculatively, less prompted to develop optimal adaptive immune response to antigenic challenges. This concept might be important as an explanation to the opposite relation often reported in concrete husbandry situations between superior performance and disease resistance (Knap and Bishop, 2000). Thus, Hcy appears as a key metabolite playing a central role at the interface between transulfuration and trans- and re-methylation, connecting dietary supplies of at least three B-vitamins and modulation of endogenous antioxidation and innate and adaptive immune responses.

Vitamins C and E: Detailed reviews on vitamin C and immune cell populations and their functions are recently provided (Carr and Maggini, 2017; Mousavi et al., 2019), showing its support to both innate and adaptive immune functions. Vitamin C (ascorbic acid) is considerably accumulated in tissues like adrenals and immune cells and is hence assumed to affect the immune functions (Schwager and Schulze, 1998). The role of vitamin C in pigs have been studied using pigs with hereditary deficiency in ascorbate synthesis, which is necessary to study the influence in relation to immune homeostasis. While ascorbate seems to exert multiple immunological functions, and is capable of preventing and treating respiratory and systemic infections by enhancing various immune cell functions, a prophylactic prevention of infection requires a dietary vitamin C intake that provides at least adequate, if not saturating, plasma levels (i.e., 100–200 mg/day) to optimise cell and tissue levels. In contrast, treatment of established infections requires significantly higher (gram) doses of the vitamin to compensate for the increased metabolic demand. It is worth noticing that, in industry practice, very often swine diets are marginally, or not supplemented with vitamin C, relying exclusively on endogenous synthesis, which is, in several occasions, not adequately supporting the requirements for immune-related functionalities.

Vitamin E is one of the most effective nutrients known to modulate immune function, which is in part due to its protective effect against oxidation of polyunsaturated fatty acids (PUFA). The regulatory role of vitamin E in the immune system and inflammation was recently reviewed (Lewis et al., 2019). Vitamin E improves T-cell-mediated functions and innate immune functions including NK cell activity and macrophage phagocytic capacity (Lewis et al., 2019). The immunoregulatory role of vitamin E has been studied in relation to respiratory infections of human and some allergic diseases such as asthma (Lewis et al., 2019) and in studies with elderly with regard to its potential to improve the overall immune response (Maggini et al., 2008). However, less is known regarding its function in relation to the gut immune system and diseases. Beyond the antioxidant function of vitamins E and C as described below, these vitamins may influence immunity by maintaining the functional and structural integrity of important immune cells and hence epithelial barrier functions.

3.2. Oxidative stress and inflammatory reactions

Oxidative stress plays a crucial role in animal nutrition and health, including the regulation of important physiological functions such as GI functionality (Celi and Gabai, 2015). Disruption of the intestinal barrier function causes deleterious effects and results in exposure of the host to luminal antigens and bacteria, leading to oxidative stress and inflammation. Oxidative stress is, by definition, an imbalance between the production of reactive species, such as peroxides and oxygen radicals, and the scavenging ability of the organism both to avoid formation and to destroy reactive species. Oxidative stress plays a dual role during infections, as free radicals protect against invading microorganisms, i.e., generation of reactive species in order to provide signals or to kill invading pathogens, but they can also cause damage during the resulting inflammation. Impaired barrier functions have been described in a number of common GI disorders in human, including IBD. In pigs, the disturbance in the intestinal barrier function around weaning typically results in enhanced mucosal exposure to bacteria and risk of infection with pathogenic bacteria, both leading to oxidative stress and inflammatory reactions. Oxidative stress arises as an actively initiated process via enzymes such as myeloperoxidase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and nitric oxide synthase (NOS), and these enzymes play crucial roles during pathogenesis. Myeloperoxidase, present for instance in activated neutrophils and lysosomes, produces hypochlorous acid from hydrogen peroxide and chloride. Hypochlorous acid is a strong oxidant capable of oxidising most biomacromolecules, i.e., bactericidal effect. NADPH oxidase catalyses oxidation of NADPH with simultaneously reduction of oxygen to superoxide. This is performed for instance by activated macrophages and granulocytes during the respiratory burst. During infection, there is an abundant activity of inducible NOS (iNOS) in macrophages and other leukocytes, and, upon its action, nitric oxide (NO) is produced (Pohanka, 2013). NO can become a very toxic substance if it meets superoxide because cytotoxic peroxynitrite is then formed, which is necessary for macrophages for their degradation of pathogens. Thus, gut inflammatory host-response produces ROS and reactive nitrogen species (RNS) which are relatively effective for killing pathogens; however, unregulated infection and even sepsis may be accompanied by extensive release of peroxynitrite. ROS can be further propagated to an uncontrolled process, i.e., peroxidation of cellular lipids. Peroxidation of fatty acids (**FA**) takes place in the body under physiological conditions; however, the production becomes excessive when homeostasis is disturbed. It has been estimated that 1% of electron flow in mitochondria is not delivered to produce water but superoxide, which has to be detoxified. Overproduction of ROS in mitochondria, for instance during infectious disease, can damage proteins, lipids and DNA, further reducing energy generation efficiency and increasing ROS production in the mitochondria (Akbarian et al., 2016). From other animal species it is shown that vitamin E, ascorbic acid, selenium, vitamin B-12 scavenge ROS (Traber and Atkinson, 2007; Traber, 2014; Liu et al., 2016; van de Lagemaat, 2019) and riboflavin are associated with ROS generation in immune cells through the priming of NADPH oxidase 2 (Yoshii et al., 2019). Hence, there may be a role for antioxidant vitamins and trace elements to control or prevent excessive oxidative reactions.

Oxidative stress is directly linked to inflammatory responses, as ROS are activators of the nuclear factor kappa-light-chain-enhancer (NF-κB) of activated immune cells. Upon stimulation by oxidants, as NF-κB-regulated proteins stimulate the production of oxidants by neutrophils (respiratory burst) and in mitochondria whereby a vicious cycle is triggered, and if not broken due to sustained and overwhelming production of oxidants, the inflammatory process becomes chronic and the body's cells and tissue are damaged. Such

free radical diseases also occur in pigs, and examples are enteritis and sepsis (and pneumonia).

Thus, it is of major importance for the gut function and animal health to control the production of oxygen species and inflammatory reactions, and vitamins E and C play major roles in relation to these reactions because of their antioxidant function within the gut epithelial layer (Lauridsen, 2019). Vitamin E (α-tocopherol) scavenges peroxyl radicals and is termed a chain-breaking antioxidant because it prevents the chain reaction of lipid peroxidation. It is localised with PUFA-enriched phospholipid domains of the cell membrane, and once the hydroxyl-group of α-tocopherol intercept with a peroxyl radical, it will reduce it to lipid hydroperoxides. Moreover, ascorbate (vitamin C) reduces the α-tocopherol radical, generating active α-tocopherol, and ascorbate is regenerated at the expense of glutathione. Lipid hydroperoxides are converted by selenium-dependent enzymes, i.e., glutathione peroxidases (Dalgaard et al., 2018), to lesser toxic hydroxides at the expense of glutathione. In pigs fed diets deficient in vitamin E and selenium, it has been reported that production of ROS, as measured by chemiluminescence, is increased, and lymphocyte response to mitogens is impaired (Lessard et al., 1991, 1993). Thus, maintenance of this antioxidant network is crucial to protect enteric cellular membranes against radical-mediated degradation, and vitamins E and C are key players in the protection of PUFA enriched in the membranes of immune cells, making them prone to oxidative damage resulting from their high metabolic activity and normal defence against pathogens. In this context it should be noted that vitamins E and C are highly concentrated in immune cells.

Moreover, heat stress can disrupt the intestinal barrier integrity through mechanisms that include inflammation and oxidative stress, and it has been observed that dietary vitamin E and selenium can maintain intestinal permeability in heat-stressed pigs (Liu et al., 2016). Besides, vitamin E supresses inflammatory factors such as proinflammatory cytokines and prostaglandin E_2 (PGE2) and may for instance reduce production of other inflammatory markers such as tumor necrosis factor alpha (TNF-α) and interleukin-6 in aged mice, particularly in response to pathogens (Lewis et al., 2019). The immune-enhancing function of vitamin C also plays an important role in the regulation of inflammatory responses (Maggini et al., 2008).

3.3. Epithelial barrier functions

The intestinal epithelial barrier mainly consists of a layer of epithelial cells joined together by intercellular junctions (Anderson et al., 1980; Cereijido et al., 1998), including specialised cells such as goblet cells that produce mucin and Paneth cells that secrete AMP (Anderson and Van Itallie, 2009). Tight junction (TJ) creates a semipermeable barrier, separating different organ compartments. Both vitamin D and vitamin A play significant roles in maintaining and stabilising the epithelial barrier function by modulating the expression of TJ proteins and intestinal transepithelial electric resistance (TER, a measurement of epithelial barrier function) during inflammatory conditions induced by enteric pathogens or microbe-associated molecular pattern such as lipopolysaccharide (LPS) (Cantorna et al., 2018; He et al., 2019; Kong et al., 2007).

In vitamin A deficiency, the integrity of the mucosal epithelium is altered, and, consequently, an increased susceptibility to various pathogens in the GIT is observed. Likewise, vitamin B-6 deficiency in growing chickens is reported to cause gizzard erosions. Both vitamins A and B-6 act as co-factors in the formation of mucin but do this in separate manners. Goblet cells appear to require retinol to synthesise mucin, and vitamin B-6 is considered critical to mucin formation because of its extensive involvement with many facets of oligosaccharide and protein synthesis (Moran, 2017). Its pivotal role relates to its use with glutamine to provide glucosamines for oligosaccharide component while interconverting many frequently limiting amino acids to optimise access for inclusion in its protein. Thus, vitamin B-6 has a more direct function in the production of individual components required for mucin formation than vitamin A.

Intestinal barrier defects are involved in several intestinal diseases in which inflammatory cytokines, ROS and pathogenic bacteria have been found to impair the TJ function. Thus, important roles of vitamins for gut function are maintaining the integrity of the intestinal mucosal and preventing inflammatory responses and oxidative stress as described above. Via these mechanisms, vitamins E and C may directly modulate certain properties of cell membranes and hence the membrane integrity and barrier function.

4. Vitamin status and effects on enteric robustness and disease resistance

Generally speaking, limited knowledge is available regarding the effect of nutritional interventions and feed additives in relation to non-invasive biomarkers (i.e., measures of animal growth, faecal and saliva samples) of the GI functionality in pigs (Celi et al., 2019) and, in fact, also in relation to clinical enteric disease responses (Roselli et al., 2017; Lauridsen and Matte, 2017). While micronutrient deficiency, especially vitamin deficiency, clearly links to infectious disease susceptibility in human, deficiency of micronutrients is rare in conventional livestock production and is not studied with specific focus on gut diseases in pigs. We would therefore like to emphasise the existing knowledge regarding vitamin nutrition, including their interaction with other bioactive nutrients or harmful components, and the *potential* link to frequently observed GI-diseases in pigs.

4.1. Interaction between vitamins and fatty acids/trace minerals

Changes in lipid metabolism are highly linked to GIT functionality and are associated to metabolic and inflammatory processes by modulating pathways in immune cells (Liu, 2015). Special emphasis is devoted to the interaction between unsaturated FA and especially vitamins exposing antioxidant activity as well as n-6 to n-3 PUFA ratio and the links with vitamins. For example, it could be expected that the level and composition of dietary fat would affect the incorporation of vitamin E into tissues and immune cells. This is true for the liver (Lauridsen et al., 2013) and mucosal immune cells harvested from lungs (Lauridsen et al., 2007); however, for the intestinal tissue it may be different with regard to α-tocopherol. In previous studies conducted by Lauridsen (2010) and Lauridsen et al. (2013), pigs were provided 5% of tallow, fish oil or sunflower oil and increasing doses of all-rac-α-tocopheryl acetate during 4 weeks

post weaning. As expected, diets supplemented with sunflower oil in comparison with fish oil increased the concentration of unsaturated fatty acids and n-6 fatty acids in the gut epithelium and mucosa. Further, dietary vitamin E supplementation increased the α-tocopherol concentration in the gut epithelium and mucosa (Lauridsen, 2010). However, dietary fatty acid composition had no influence on the total α-tocopherol concentration, and dietary vitamin E has no influence on fatty acid in the gut epithelium and mucosa in the experimental conditions used (Lauridsen, 2010). But it should be kept in mind that the intestinal changes in PUFA composition enhance the requirement for antioxidative protection, and in this context α-tocopherol and vitamin C are important for the membrane protection and hence for the epithelial barrier function and gut health. Inclusion of vegetable oils instead of animal fat contributes with high levels of unsaturated FA to increase the susceptibility towards oxidation. Fatty acid peroxides represent an ongoing threat because of their unhindered passage through the mucin network (Moran, 2017). Once formed, the fatty acid hydroperoxides exert the potential to impair the absorptive cellular membranes (Lauridsen et al., 1995). Hence, any increase in the dietary proportion of unsaturated FA would require antioxidant protection. Vitamin E and retinol provide significant protection from hydroperoxides harmful to membranes beyond benefits offered by supplemental antioxidants such as synthetic antioxidants (butylhydroxytoluene, butylhydroxyanisol and ethoxyquin) or the more frequently studied natural ones (such as polyphenols as reviewed by Surai (2013)). Therefore, when no severe oxidative stress is induced, there may not be any measurable links between these antioxidant vitamins and serum lipid peroxides (Negishi et al., 1999).

Addition of antioxidants to the diet minimises the loss of vitamins A and E by acting as the preferred ROS quenchers when in direct association with one another during digestion. Hence, the potential of using antioxidative substances or plant extracts or feed ingredients containing substances such as polyphenols exposing antioxidant properties should probably be seen more as a tool to protect the vitamins during digestion and absorption processes in the gut. With regard to vitamin E, the natural occurring γ-tocopherol in vegetable oils and other feed ingredients would protect the supplemented α-tocopherol during hydrolysis of the ester bond, allowing α-tocopherol to be protected from being oxidised during the digestive processes in the GIT.

Although tissue defence mechanisms against free radical damage generally include vitamin E, vitamin C and β-carotene as major antioxidant sources, there are several other micronutrients which also play a critical role in protecting the internal cellular constituents from oxidative damage. For instance, the bioavailability of selenium is critical for the function of glutathione peroxidase (GSH-Px) (Dalgaard et al., 2018), and copper, zinc and manganese are important for the function of the metalloenzyme superoxide dismutase, and iron for the catalase. The intestinal tissue balance of FA and the antioxidant activity of vitamins and trace minerals are important for the protection against free radical damage. In weaned pigs, high dietary Zn levels improved the small intestinal redox state by increasing the ratio of reduced glutathione to oxidised glutathione, (Slade et al., 2011), and, unlike most other minerals, Cu and Zn have antibacterial properties causing beneficial effects on gut health of pigs, and they are therefore often added to diets in quantities greater than what is needed to fulfil the nutritional requirements (Liu et al., 2016). For the Se-dependent GSH-Px, the metabolism of oxidised and reduced glutathione, as well as the enzyme GSH-Px activation, is closely related to amino acids cysteine and methionine via the key intermediary metabolite Hcy as mentioned before. In fact, the generation of ROS and peroxides from activated metabolism would up-regulate transulfuration and down-regulate trans-methylation (Mosharov et al., 2000), directing Hcy towards synthesis of cysteine and eventually to glutathione. Therefore, there is a retro-control of oxidative metabolites for their catabolism via the transulfuration pathway. The animal metabolism does not distinguish between sulphur forms of methionine and cysteine and their Se analogues (Daniels, 1996). Under oxidative pressure, both forms of cysteine and Hcy are regulated by redox changes just like their sulphur forms (Bueno-Dalto and Matte, 2017). The transulfuration pathway directs sulphur forms towards more glutathione synthesis and seleno forms towards more selenocysteine metabolites activating GSH-P ×. The full efficiency of the transulfuration (transelenation) pathway is central for this metabolic process which is well-recognised as dependent upon adequate cellular levels of vitamin B-6 (Yasumoto et al., 1979). The importance of B-6 for an adequate flow of organic Se (Se-cysteine) towards the GSH-Px system in response to a pro-oxidative stress was demonstrated recently in the pig model (Bueno-Dalto et al., 2015). In fact, gene expressions of GSH-Px in cell cytosol of both liver and kidney cells were at least 50–100% greater in gilts fed a dietary organic source of Se supplemented with B-6 vs not supplemented with B-6. Therefore, vitamin B-6 is crucial for the fate of organic Se towards the GSH-Px system and probably for the enzymatic reactions leading to the incorporation of selenocysteine into various selenoproteins.

4.2. Vitamins and link to frequent GI diseases

While several of the above-mentioned mechanisms by which vitamins influence host immunity, inflammation and oxidative stress have been reviewed in relation to human GI diseases, little is known with regard to the impact on frequently observed production diseases in the GIT of pigs, i.e., gastric ulcers and colibacillosis.

4.2.1. Gastric ulcers

Ulceration generally occurs due to disturbance of the normal equilibrium caused by either enhanced exposure to aggressive factors or diminished mucosal resistance. Gastric ulceration in swine is considered a multifactorial disease, i.e., several factors may contribute to the pathogenesis of the mucosal lesions, and *Helicobacter Suis* may be a contributing factor. Generally speaking, very little focus has been dedicated to the stomach when considering the role of vitamins for the gastric mucosal function. However, it should be noted that mucosal function is a condition for the absorption of vitamin B-12 (Franceschi et al., 2014). This vitamin is unique among other vitamins and micronutrients in that an additional factor is required to enable its absorption from the gut, namely the intrinsic factor (Okuda, 1999). The cells in the upper part of the stomach are classified as the parietal or oxyntic cells which, in addition to hydrochloric acid, secrete this gastric intrinsic factor, a glycoprotein that binds B-12. This step is necessary for the subsequent absorption of this vitamin in the small intestine. Furthermore, it has been suggested in human that there is an association between *Helicobacter pylori*

infection, reduced cobalamin absorption and cobalamin status and, consequently, elevated Hcy levels (Dierkes et al., 2003).

Other nutrients may exert a role in the prevention and probably healing of gastric ulceration via anti-inflammatory and immunomodulatory mechanisms. The dietary balance of n-6 and n-3 FA in terms of inflammatory reactions, and the anti-inflammatory and antioxidative effects of vitamins and trace elements have been given special attention in relation to enhancement of gastric ulcer healing in swine. This impact is related to the role of prostaglandins in the development and healing of gastric ulcer in the glandular regions as well as the influence of FA peroxides, which may be enhanced because erosion of mucosal gastric cells may make the pig stomach more vulnerable to oxidation. According to Obel (1953), stomach ulcers in pigs produced by diets containing 6% cod liver oil might possibly be caused by peroxide formation from unsaturated FA in the absence of vitamin E. In the studies by Nafstad (1967) and Nafstad and Tollersrud (1967), a slight but not significant degree of protection against gastric lesions was afforded by vitamin E supplementation. However, more evident was the increased severity of lesions when vitamin E was omitted from the ulcerogenic diets fed to the pigs. In addition, deficiency of other antioxidative nutrients may provoke ulceration through increased peroxide generation; for example, deficiency in selenium may decrease the activity of glutathione peroxidase and result in increased cellular peroxides.

4.2.2. Colibacillosis

Weaning of piglets generally increases the risk for GI infections, mainly *E. coli*-associated diarrhoea 'colibacillosis' (Heo et al., 2013; Fleury et al., 2017; Gresse et al., 2017; Moeser et al., 2017; Pluske et al., 2018). The activation of the immune system during infection alters the partitioning of nutrients from deposition of body proteins to synthesis of immune molecules (Kim et al., 2016), and the presence of exogenous and endogenous pyrogens provokes inflammatory responses and fever (inhibiting of appetite and vomiting action). Overall, these inflammatory responses are caused by pro-inflammatory cytokines and subsequent synthesis of the immune-suppressive molecules during the resolution phase such as PGE_2 (Calder, 2006; Buckley et al., 2014). Resolution and clearance of cellular debris from mucosal surfaces involve the essential PUFA-derived mediators as well as activated antimicrobial mechanisms in mucosal epithelial cells (Buckley et al., 2014). Several research experiments have been conducted during the last decades with the aim to investigate the effect of specific nutrients and feed additives to enhance and support different aspects of gut health after weaning (Lauridsen, 2019). While many studies have developed conclusions on the basis of proxy indicators of gut health (Roselli et al., 2017; Lauridsen and Matte, 2017), very few studies have investigated the potential link between vitamins or the host vitamin status and robustness of porcine enteric infectious diseases such as generation of colibacillosis diarrhoea. Interestingly, however, Pluske et al. (2018) recommended in their review that gut health-enhancing diets for pigs in the post-weaning period may incorporate, amongst others, supplementation with 150–200 mg/kg feed vitamin E and other antioxidants such as selenium or essential oils and phytogenic substances with antioxidant capacity, and a minimised n-6 to n-3 PUFA ratio. These recommendations regarding vitamin E, antioxidants and fatty acids are based on research as referred to by Kim et al. (2016) and Shin et al. (2017), respectively. With regard to vitamins D and A, the presence of research focusing on their impact for prevention of human intestinal diseases (IBD and colitis) and the impact of B-vitamins in various pathways of cell metabolism reveals a potential role for these vitamins in relation to colibacillosis diarrhoea.

The mechanisms by which vitamins potentially can prevent *E. coli* infection or colibacillosis are summarised in Table 2. Below, a more detailed explanation is given on the impact, focusing on pig gut health.

As described above, longer-chain FA and antioxidant activity influence pigs' immune responses. Vitamin E and selenium may help cells to survive toxic products that are produced in order to efficiently kill ingested bacteria. Besides, if immune cells are enriched with n-6 FA, α-tocopherol is capable of reducing the harmful inflammatory cascade through antagonising peroxidation of arachidonic acid (ARA) (Upadhaya et al., 2015) located in the phospholipids of the cellular membrane. Once liberated, ARA may be converted to PGE_2 by cyclo-oxygenase 2 or other eicosanoids, or it may be oxidised through the contact with ROS. Hence, in diets rich in n-6 FA, such as corn or barley-based feed, vitamin E may exert a beneficial role via the inhibition of the ARA cascade. A similar, though indirect, effect

Table 2
Summary of mechanisms by which vitamins potentially can inhibit enteric infection (colibacillosis) in pigs.

Mechanism	Vitamin (or bioactive forms)	Impact
Inhibition of inflammation (mainly arachidonic acid-derived inflammation (reduction of PGE2 production))	B-vitamins, vitamin E	Inflamed gut appears to provide a favorable environment for ETEC
Control of oxidative stress	Vitamins with antioxidative activity	Prevention of excessive production of reactive oxygen species during an host-inflammatory induced response, and hence prevention of enteric infection.
Improvement of effective immune cell activity and response, and immune cell homeostasis	Vitamins E, C, A, D and B-complex	Formation of immune cells and their signals and modulation of immune cell responses.
Improvement of intestinal barrier function	Vitamins D and A	Regulation of tight junction molecules and hence prevention of barrier damage
Regulation and modulation of innate and adaptive immunity; resolution of inflammation	Vitamins A and D	Gut homing, immune cell differentiation and cytokine suppression are important host responses to injury and infection and resolution of inflammation.
Production antimicrobial peptides	Vitamins A and D	Enhanced innate immunity and shaping of commensal microbiota
Shaping the microbiome	Thiamin, riboflavin, and vitamins A, B-6, B-12, C, D, E and K	Regeneration of commensal microbiota

has been attributed to the three B-vitamins, B-6, folic acid and vitamin B-12, through their role in metabolic disposal of Hcy (Signorello et al., 2002) as high levels of this intermediary amino acid stimulate the release of ARA and produce thromboxane B_2 and ROS accumulation, leading to an unbalance in the redox state in platelets. Likewise, reduction of Hcy through the action of vitamin B-6, folates and B-12 could contribute to restoring the arachidonic homeostasis and redox balance. Other modes of action of vitamins have been reported for instance in chickens where vitamin E deficiency reduced the phagocytic activity of macrophages and neutrophils, whereas large doses of vitamin E or vitamin A could protect the host against mortality from *E. coli* with increased phagocytosis and antibody production (Tengerdy and Brown, 1977). In addition, vitamin E deficiency has been found to predispose pigs to different diseases including *E. coli* infection (Ellis and Vorhies, 1976). In post-weaning piglets inoculated with *E. coli*, Lauridsen et al. (2011) observed a dramatic reduction in the liver α-tocopherol concentration, probably indicating an enhanced consumption of the vitamin for the phagocytic activity upon *E. coli* infection. Vitamin E supplementation (300 mg/kg feed) reduced the concentration of PGE_2 in plasma of pigs challenged with LPS intramuscularly; however, provision of n-3 FA exerted a greater effect, and no additive effect between the combination of vitamin E and n-3 FA was observed with regard to anti-inflammatory responses (Upadhaya et al., 2015). Scientists from the same group (Kim et al., 2016), in a subsequent study with pigs, show that vitamin E reduces acute inflammatory responses in weaned pigs experimentally infected with an ETEC. α-Tocopherol is easily incorporated into cellular membranes upon dietary supplementation (Lauridsen and Jensen, 2012), and, for instance in pigs, the increasing doses of vitamin E in the weaning diets are reflected by increased amounts of α-tocopherol in epithelium and mucosa 3 weeks after (Lauridsen, 2010). Thus, manipulating the concentration of vitamin E in immune and epithelial cells of pigs may be used as a nutritional strategy, especially during enteric infectious disease conditions involving inflammatory and oxidative stress reactions.

Little is known regarding the quantitative need for vitamins for supporting optimal development of innate and adaptive immune responses. In general, chronically severe deficiencies of micronutrients are more debilitating to the development of the immune system than macronutrients such as energy and protein (Klasing, 1998). One of the major changes at weaning is nutrition, i.e., the change from sow milk to solid feed. Creep feed, as commonly applied in many countries, is provided from around 14 days of age, but a significant creep feed intake is not observed until approximately 4 weeks of age. When milk supply ceases abruptly, the structure and function of the digestive tract begin to change within hours (Lallès et al., 2007a, b), the microbiota becomes unstable (Jensen et al., 1988) and the yet immature piglet's immune system is challenged by new feed antigens and commensal bacteria. Weaning stress and increased exposure to intestinal bacterial populations and pathogen-associated molecular patterns contribute to inducing an acute phase response, reducing the piglet's appetite and normal nutrient intake and disrupting digestion and absorption. Klasing (1998) mentioned that nutrient deficiencies that are especially damaging to the development of the immune system include linoleic acid, vitamin A, iron, selenium and several of the B-vitamins. In addition, more recent research exploring the importance of vitamin D and immune cell function (as overviewed e.g. by Weiss and Schaible (2015), and vitamin C and immune function (Carr and Maggini, 2017) indicated that deficiency of these vitamins may also be included to the list of nutrient deficiencies that can be especially harmful. It is plausible that the systemic acute phase response accompanying most infectious challenges is a more significant consumer of nutrients than the immune system itself. Given the importance of vitamins on several mechanisms of importance during infection, including their indirect and direct influences on immune function and system, future studies on impact of vitamin nutrition on enteric disease resistance in pigs are required in order to develop strategies for vitamin nutrition to combat infectious diseases.

5. Critical phases of vitamin nutrition for pigs in relation to gut function and health

Beyond the role of vitamins for development of the enteric immune system and hence on robustness and disease resistance, their function for pig resilience should be considered, i.e., the capability of the pig to maintain productivity during a challenge, for instance caused by oxidative stress, inflammation or dysbiosis. While dysbiosis (Adhikari et al., 2019) is frequently observed in pigs post weaning (Gresse et al., 2017), there are especially two critical periods with regard to the risk of oxidative injuries in piglets: the first week of life and the first few weeks after weaning. During these periods, piglets' redox balance may be disrupted, and hence they can be more vulnerable to oxidative injuries. In addition, the farrowing process may be stressful to both dams and neonatal piglet, especially after prolonged parturitions that may produce hypoxia in foetal pigs from frequent uterine contractions during birthing. Breeding for hyper prolific sows may have exacerbated this issue, as large litter sizes may enhance the risk of prolonged parturitions. Moreover, as the proportion of low birth weight piglets increases with selection for larger litters, this selection has resulted in greater number of piglets with poor performances and increased losses before weaning, due to higher risk of mortality and infections. Indeed, recent studies indicate that the expression of genes associated with immunity and oxidative stress in piglets' intestinal tissue are exacerbated in low birth weight piglets compared to high birth weight piglets (Lessard et al., 2018), and the establishment of neonatal gut microbial populations in piglets during the lactation period differed between the two groups (Morissette et al., 2018). Furthermore, genetic background also influences the oxidative stress level of pigs, as breeding towards lean type pigs has resulted in chronic oxidative stress conditions causing poor homeostatic control of inflammatory responses (Amadori and Zanotti, 2016). Overall, the results of the study by Adhikari et al. (2019) suggested that gut microbiota undergoes significant changes during the post-weaning period, becoming more stable as the post-weaning age increases. Hence, when addressing the effect on vitamin interventions on gut health and function, it is obvious to emphasise these critical periods of the piglets' life: after birth and during the post-weaning period.

5.1. Vitamins and importance for postnatal immune development

The postnatal development of the immune system is important for establishing an effective immunological response towards

nutritional and microbial antigens that are present in the gut (Rothkötter et al., 2002), and vitamins play an important role for the development and maturation of the enteric immune system. Pigs are born agammaglobulinemic (i.e., that maternal antibody cannot be transferred from sow to the piglet in utero) because of the structure of the placenta (Poonsuk and Zimmerman, 2017). They are also born with an immature immune system and very limited cell-mediated immunity, i.e., few peripheral lymphoid cells, poor development of lymphoid tissues and no effector and memory T-lymphocytes. Thus, piglets must be supplemented by maternal immune components during the first month of life to protect against infectious agents. Besides major nutrient components (including vitamins and trace minerals), porcine milk contains antimicrobial and immunomodulatory elements which are compensating for the immature neonatal immune system by contributing to the protection of piglets against environmental infectious pathogens and to the development of the immune system and the gut microbiota (Turfkruyer and Verhasselt, 2015; Mohanty et al., 2016; Pacheco et al., 2015; Zhang et al., 2018a). The supply of immunomodulatory substances can be circulating mucosal antibodies and immunoregulatory factors derived from colostrum and milk, and immune cells provided in mammary secretions. Vitamin supplementation of the sow may facilitate the passive immunisation of piglets by increasing the concentration of antibodies in sow colostrum and milk. However, results are inconsistent. Injection with 1000 IU of vitamin E to sows on day 100 of gestation increased the IgG concentration (Hayek et al., 1989) while other authors suggested that vitamin E supplementation did not improve IgG and IgA contents in sow colostrum and milk (Nemec et al., 1994; Pinelli-Saavedra et al., 2008). Lauridsen and Jensen (2005) observed an improved specific antibody response to *E. coli* in serum of piglets post weaning with increasing dietary vitamin E treatment of sows. These results may indicate that α-tocopherol transfer to the off-spring via milk may be beneficial for the development of their immune system. Probably the effects are difficult to estimate because of the high variation between individuals within a litter in terms of body weight and weight at weaning as well as individual colostrum intake. Vitamins A and D also play a major role in the development and maturation of the immune system after birth. Preterm and low birth weight infants have low levels of these nutrients and are at risk of developing detrimental health consequences associated with vitamin A and vitamin D deficiencies (Murguia-Peniche, 2013). However, maternal vitamin D supplementation, in the form of $25OHD_3$, had no influence on the concentration of immunoglobulins in colostrum and milk from sows, but gut bacterial metabolites of the hindgut were affected in suckling pigs (Zhang et al., 2019). To the best of our knowledge, there is no information available on the impact of vitamin B supplementation to sows' diet on colostral immunoglobulins. In other species with the same type of placentation (epitheliochorial) such as dairy cows, it has been reported that colostral IgG concentrations may be increased by up to 18 % after nicotinic acid supplementation during the last month of gestation (Aragona et al., 2016). However, in reports where supplementations with other vitamins such as β-carotene, biotin and/or folates and vitamin B-12 were administered before parturition, no effect was observed on IgG concentrations in the colostrum (Kaewlamuna et al., 2011; Duplessis and Girard, 2019).

5.2. Transfer of vitamins to off-spring

In terms of vitamin transfer, the efficacy of in utero-placental transfer of vitamins from dams to foetuses and to new-born piglets varies from one vitamin to another (Matte and Lauridsen, 2013). While the transfer of vitamins C and vitamin B-12 is important during pregnancy (in utero), piglets are born deficient in fat-soluble vitamins (Matte and Audet, 2019). For example, even if the gestating sow has a high plasma vitamin E status, the piglets are born with almost no vitamin E content (Lauridsen et al., 2002) due to the limited placental transfer. Timely colostrum intake is crucial for piglets to gain not only sufficient immunisation but also vitamins and other nutrients. During the first few hours after birth, the piglet's intestine is able to absorb macromolecules in a non-selective way; however, a rapid 'closure' of the gut for macromolecule uptake (IgG and vitamins) happens 24–48 hours after birth (Rothkötter et al., 2002). Thus, the postnatal immunological development is highly correlated to adequate colostrum intake during the first 48 h, and this also applies to all vitamins in the newborn pig (Matte and Lauridsen, 2013). The colostrum transfer is very efficient as shown, for example, for colostrum vitamin A and α-tocopherol, which is highly reflected in the sow's colostrum level and piglet's plasma status (Lauridsen et al., 2002; Lauridsen and Jensen, 2005). The vitamin status of the sow is important for the provision of vitamins to the sucking neonate, and the vitamin supply of the off-spring is important for the regulation and development of innate and acquired immune responses. Although vitamin E deficiency is rare in human (as well as in pigs), vitamin E supplementation above current dietary recommendations has been shown to enhance the function of the immune system and to reduce the risk of infection, especially in older individuals (Lewis et al., 2019). With regard to vitamin D, Goff et al. (1984) demonstrated that the $25OHD_3$ of the neonate is largely correlated to the $25OHD_3$ status of the sow at birth, and $25OHD_3$ has clearly been demonstrated as the key vitamin D metabolite associated with transplacental transfer (Haddad et al., 1971). However, dietary treatment of the sow with vitamin D (200−2,000 IU vitamin D_3/kg feed) was not a good nutritional strategy to increase the suckling piglet's vitamin D status analysed as $25OHD_3$ in plasma (Lauridsen et al., 2010). Experiments with sows (Witschi et al., 2011; Weber et al., 2014; Flohr et al., 2016) demonstrated elevated milk concentrations of $25OHD_3$ with increased dietary vitamin D_3; however, effects varied depending on parity and sampling day of the lactating sows, and although the increased dietary vitamin D supplementation of the sows was also reflected in the plasma $25OHD_3$ concentration of the suckling piglets, their vitamin D status was below 10 ng/mL. Considering the more recent studies on vitamin D supplementation for sows in relation to the effect on the vitamin D status of the suckling piglet, they seem to come to the same conclusion: that the transfer of vitamin D from the sows to the off-spring is not that efficient (Matte and Lauridsen, 2013), at least when considering $25OHD_3$ as the indicator of vitamin D status.

5.3. Challenges in vitamin nutrition during early weaning

Pigs do not become fully immunologically competent until about 4 weeks of age (Poonsuk and Zimmerman, 2017). However, this is

probably very variable, and, in terms of cell-mediated immunological maturity, higher ages are considered (Blecha et al., 1983). In fact, the weaning of the piglet from the sow at 28 days of age, as practiced in many swine-producing countries, takes place when the piglet is in a so-called 'immunological gap', i.e., when passive immunity levels are still off and adaptive immunity is not strong enough to provide adequate protection through humoral and cellular immune responses (Devillers et al., 2007). Although not considered in many research studies, the immunological maturity may depend on other factors such as birth weight and colostrum/milk intake (Lauridsen and Matte, 2017; Lessard et al., 2018). In the following, the consequences of early weaning in terms of microbiota dysbiosis, intestinal barrier defects, absorptive function and enteric nervous system disturbance are emphasised with regard to vitamin nutrition.

5.3.1. Microbiota dysbiosis

Early weaning at 3–4 weeks of age implies a risk for pig health, and this is the reason why oral antibiotic treatments are frequently applied in this phase. Many studies (in human and murine) have shown that exposure to antibiotics can cause gut microbiota dysbiosis. Antibiotic infusion in the ileum of growing pigs affects jejunal and colonic specific bacteria counts, and correlation analysis revealed that change in the intestinal microbiota (provoked via antibiotic infusion in the ileum) was correlated with alterations in immunoglobulin and cytokine concentrations in jejunal and colonic mucosa and serum at 45 days of age (Zhang et al., 2018b). In another study from the same group (Mu et al., 2017), a profound effect of oral antibiotics has been observed primarily in the foregut microbiota, but it has limited effect on the microbiota and function in the large intestine; this observation could be attributed to a gradual dilution of antibiotics in the gut (Zhang et al., 2018b). Hence, antibiotic treatment may induce changes in the intestinal microbiota throughout the GIT that may affect the synthesis of vitamin K and B-vitamins and probably also the absorption of fat-soluble vitamins as described above.

5.3.2. Intestinal barrier defects

Intestinal barrier defects are involved in human intestinal and metabolic diseases such as inflammatory bowel disease and obesity which are accompanied by an increase in inflammatory cytokines, ROS and pathogenic bacteria (Suzuki and Hara, 2011). The same mediators are involved in an impaired intestinal barrier function or an increased intestinal permeability in piglets after weaning (Wijtten et al., 2011; Gresse et al., 2017) and influence not only the expression but also the cytoskeletal association of tight junction proteins through activation/inactivation of intracellular signalling.

5.3.3. Absorptive functions

Early weaning may influence vitamin absorption in pigs. In general, active small-intestinal absorption decreases after weaning when pigs are weaned at 3 weeks of age or at a younger age (Wijtten et al., 2011), and impaired capacity for absorption may in fact lead to reduced vitamin status since many of the vitamins are actually absorbed in the small intestine. However, the vitamin A status may not be affected on the short term if adequate vitamin A depots are established during the suckling period. Early weaning may also reduce the capability to absorb vitamins from the diet because of the impaired enzymatic activity of the GIT of the pig. Lack of lipases after weaning reduces the digestion of fat and therefore the absorption of fat-soluble vitamins. In addition, hydrolysis of vitamin esters supplemented to feed may be reduced during the post-weaning period because of impaired activity of carboxylic ester hydrolase (Lauridsen et al., 2001).

5.3.4. Enteric Nervous System function

Early weaning of piglets from the sow may also lead to disturbances in the Enteric Nervous System (ENS) function that can have a deleterious impact on the GI health (Moeser et al., 2017). The ENS contains >100 million neurons, which is as many as in the spinal cord, and plays a central role in the gut and overall systemic health. As reviewed by Moeser et al. (2017), major changes take place during the postnatal life, and although the influence of weaning on ENS has not been extensively studied in the pig, there is a growing evidence that disturbances in the ENS can have deleterious impacts on the GI health. Moreover, there are several indications from research in human and animal species that vitamins play an important role for the postnatal development in ENS. An important biochemical action is via the synthesis of acetylcholine, which is controlled via the enzyme choline acetyltransferase (ChAT). Cholinergic neurons represent an important neuronal system that exhibits significant developmental changes, and the proportion of choline acetyltransferase expressing neurons increases dramatically in the postnatal life. There are several examples from vitamin research in rodents showing that vitamin deficiencies, e.g. vitamins B-12, A, D and E, and/or supplementation affects the cholinergic activity in the central nervous system of rodent models. Less is known regarding the global link between the ENS and the role of vitamins; however, since the cholinergic innervation of the gut is represented by the abundant ChAT neurons, an effect of vitamins in relation to the ENS may be expected. For instance, the developing nervous system appears to be especially vulnerable to vitamin E deficiency like in new-born children, whereas, in contrast, individuals who develop GI disorders affecting the vitamin E absorption in adulthood may not develop neurologic symptoms for 10–20 years (Traber, 2014). Other studies on rodent models support the role of vitamins in the development and/or functionality of the ENS (Fu et al., 2010; Larsson and Voss, 2018; Zanoni and Hermes-Uliana, 2015). It is plausible that vitamins also have a major influence on the development of ENS of pigs. Reduced supply due to either limited colostrum or milk per se or reduced feed intake upon weaning may lead to subclinical deficiencies and could impair the development of the ENS in piglets and eventually interfere with their normal animal behaviour development and physiological responses.

6. Conclusion and perspectives

Recent advances in vitamin research have shown that these micronutrients are essential for the gut function and its development. A considerable number of studies have been performed with regard to the role of vitamins for gut functionality, health and disease prevention in human; however, considerably fewer studies are available in livestock, including pigs. While the role of the commensal microbiota is often focused on the production of vitamin K and B-group vitamins, the bacterial vitamin usage and influence of exogenous factors such as vitamin supplementation or antibiotic treatment on the commensal microbiota is less addressed and may call for more attention in future pig production. Vitamin D influences the composition of the gastrointestinal microbiome, and the immunomodulatory role of vitamin D is increasingly recognised, calling for more research on the vitamin D metabolites in relation to the gut functionality in pigs. Antioxidant vitamins (primarily vitamins E and C) have in general been shown to play a major role for immunity and health of livestock, but very little research is available regarding the impact of these vitamins, as well as others from the B-complex, in relation to porcine gut health and function. Like vitamin D, vitamin A has a strong influence on the intestinal immune regulation, and deficiencies of these vitamins seem to be linked to impaired intestinal barrier function. B-vitamins mainly have an indirect effect on immune function of the gut and their interaction with bacterial cells and network within the gut. While vitamin deficiency in humans is still a frequent problem in many countries, vitamin deficiency is generally not a problem in modern intensive pig production. However, due to the rapid genetic improvement and the intensive production methods, the modern pig is often exposed to challenges that lead to disrupted redox balance and uncontrolled inflammation. Hence, there is an increased demand for control of reactive oxygen species and peroxides, and therefore antioxidant vitamins may be considered a strategy for enhanced enteric immunity and inflammation control. Further, in case of limited colostrum intake, vitamin supply may be critical for piglets soon after birth, and a transient lack of vitamin nutrition may also appear post weaning due to the limited feed intake and impaired digestive functions. Since these transition periods are highly important for the gut development and its functionality, these critical periods of the pig life should be emphasised with regard to vitamin nutrition. While several research papers address the role of Zn and Cu in relation to the gut functionality of the pig, and the use of these trace elements as alternatives to antibiotics, the role of vitamins is much less considered in relation to gut health and function of pigs although they share a lot of similar functions with Zn and Cu. We therefore suggest future research and development of alternative strategies to antibiotics and medicinal zinc-oxide to emphasise the role of vitamins for gastro-intestinal functionality, health and disease prevention in pigs.

Declaration of Competing Interest

The authors declare that they have no conflict of interest. Charlotte Lauridsen prepared and created the initial draft, co-authors provided their inputs, commentaries and revisions. All authors read and approved the final manuscript.

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