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The role of vitamin A in non-ruminant immunology

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Vitamin A (retinol) is an essential micronutrient with a crucial role in the immune system of non-ruminant animals, such as swine and poultry. It includes three chemical compounds with distinct properties and functions in the body: retinol, retinal, and retinoic acid. In monogastric feed, vitamin A is primarily present in the form of retinyl esters. The metabolism of dietary vitamin A esters involves their conversion to retinol, which is then transported to different tissues and cells for further metabolism into active forms such as retinoic acid. These active forms of vitamin A have been found to play a crucial role in regulating both innate and adaptive immune responses. Specifically, they are involved in the differentiation, proliferation, and function of immune cells such as T and B lymphocytes, as well as dendritic cells. Vitamin A deficiency can lead to impaired cellular immunity, reduced antibody production, and consequently an increased susceptibility to infections. In swine and poultry, hypovitaminosis A can also affect gut-associated lymphoid tissues, leading to gut-related health problems and compromised growth performance. On the other hand, vitamin A supplementation has been shown to have immunomodulatory effects on non-ruminant immune responses. By administering or supplementing retinol, immune cell proliferation, antibody production, and cytokine secretion can be enhanced, which can ultimately result in improved immune function and disease resistance. Therefore, vitamin A has potential applications as an immuno-micronutrient for improving health and preventing diseases in swine and poultry. However, the optimal dosage and timing of vitamin A supplementation need to be carefully determined based on the specific requirements of different non-ruminant species and their production stages. Overall, a better understanding of the role of vitamin A in non-ruminant nutritional immunology could have significant implications for animal health and productivity and could inform the development of effective dietary strategies to optimize immune function and prevent diseases in swine and domestic fowl. This review paper aims to offer valuable insights into the role of vitamin A in the nutritional immunology of non-ruminants while also emphasizing the current gaps in knowledge and potential areas for further research.

KEYWORDS

vitamin A, retinol, non-ruminants, swine, poultry, supplementation, immunity

1 Introduction

Vitamin A is an essential micronutrient that cannot be synthesized by non-ruminants and must be obtained through the diet. Although certain plant pigments called carotenoids may yield retinoids metabolically, only a small percentage of them can be converted into vitamin A precursors in mammals and birds (Surai et al., 2003; Combs and McClung, 2017). Due to practical considerations, the naturally occurring vitamin A and carotenoid levels in feed ingredients are not typically taken into account during diet formulation, and instead, the total retinol requirement is satisfied through dietary supplementation of retinyl acetate (Darroch, 2000).

Vitamin A refers to three distinct chemical compounds, each with unique properties and functions in the body: retinol, an alcohol; retinal, an aldehyde; and retinoic acid (Carazo et al., 2021). As a fat-soluble vitamin, retinol is required for a range of biological processes, including vision, reproduction, growth, and development, but perhaps most importantly, it is essential for immune system function (Huang et al., 2018). The immune system defends the body against pathogens and other harmful substances, and vitamin A is known to modulate the immune response (Gürbüz and Aktac, 2022). A deficiency or suboptimal supply in retinol can lead to an increased susceptibility to infections and a compromised immune system function (Ahmad et al., 2009). Therefore, understanding the role of vitamin A in nutritional immunology of non-ruminants is critical for improving animal health and productivity, as well as for developing effective dietary strategies to optimize vitamin A supply.

When it comes to meat consumption, pork and poultry account for 75% of land animals consumed worldwide (den Hartog and Ravindran, 2019). This translates to approximately 16% of the dietary protein contribution in humans (Smith et al., 2022). Meanwhile, in both children and adults, eggs have been identified as a cost-effective source of protein delivery, contributing approximately 2.7% and 3.7% of the total dietary protein intake, respectively (Papanikolaou and Fulgoni, 2020). Therefore, optimizing immune system function in pigs and poultry is important for several reasons. Firstly, it helps to ensure animal welfare by reducing the risk of disease and minimizing the need for antibiotics, which can have negative effects on animal health and food safety. Secondly, a healthy immune system can improve production efficiency, leading to better growth rates and meat quality, which in turn can benefit farmers and consumers (Niu et al., 2022). Furthermore, reducing disease in livestock can also have a positive impact on human health by reducing the risk of zoonotic diseases (Thumbi et al., 2015).

This review paper aims to provide a comprehensive overview of the current state of knowledge on the interaction between vitamin A and the immune system in non-ruminant animals. Specifically, this review will cover the following topics: (1) the metabolism and functions of vitamin A, (2) the impact of vitamin A deficiency on non-ruminant immune function, (3) the immunomodulatory effects of vitamin A supplementation, (4) effect of hypervitaminosis A on immune function and (5) the potential applications of retinol as an immuno-micronutrient for improving health and preventing diseases in swine and poultry.

Overall, this review paper is intended to provide valuable insights into the role of vitamin A in nutritional immunology of non-ruminants and highlight the current gaps and opportunities for further research in this field.

2 Vitamin A metabolism and function

The digestion and absorption of dietary vitamin A occur in the small intestine of birds and mammals. Retinol is released into the intestinal lumen when pancreatic esterases hydrolyze vitamin A esters (Reboul, 2013). After hydrolysis, retinol is incorporated into mixed micelles comprising of bile salts and other lipids, which facilitates efficient absorption. Once absorbed, the retinol is re-esterified in the enterocytes and integrated into chylomicrons, which then enter the lymphatic system and bloodstream transporting vitamin A to the liver (O'Byrne and Blaner, 2013). Vitamin A is stored as retinyl esters in hepatocytes, stellate, and parenchymal cells, which are specialized cells found in the hepatic system (Haaker et al., 2020). When needed, retinyl esters are hydrolyzed to release retinol, which can then be transported to target tissues *via* plasma retinol-binding protein (RBP) through complexation with transthyretin (Raghu and Sivakumar, 2004; Steinhoff et al., 2022). Cells that express the membrane protein STRA6 mediate the cellular uptake of retinol by taking up the retinol-RBP complex (Kelly and von Lintig, 2015). Within the cell, vitamin A is usually converted into its active form, retinoic acid, by two sequential oxidation reactions catalyzed by retinol dehydrogenases and retinal dehydrogenases (Bchini et al., 2013).

Retinoic acid is the active form of vitamin A, which binds to nuclear receptors such as retinoic acid receptors (RARs) and retinoid X receptors (RXRs) to exert its biological effects (McKenna, 2012; Al Tanoury et al., 2013). RARs and RXRs form heterodimers that bind to specific DNA sequences and regulate the transcription of target genes (le Maire et al., 2019). Co-regulatory proteins such as co-activators and co-repressors can modulate the transcriptional activity of RARs and RXRs (Cordeiro et al., 2019). The RAR-RXR heterodimer controls the expression of target cistrons involved in various physiological functions such as vision, immunity, and cell differentiation (Li et al., 2021).

The importance of vitamin A in vision lies in its role as a fundamental component of the visual pigment rhodopsin. Rhodopsin is located in the retinal rods and is crucial for vision under low-light conditions (Park, 2014). Light striking the retina results in a conformational change in rhodopsin, leading to the initiation of a signaling cascade that ultimately culminates in visual perception (Palczewski, 2014). Rhodopsin is made up of two components: opsin, which is a protein, and 11-cis-retinal, the chromophore that is derived from retinol (Ortega and Jastrzebska, 2019). Consequently, if left untreated, a deficiency of vitamin A may result in night blindness and ultimately progress to complete blindness in animals (Debelo et al., 2017).

One of the most important functions of vitamin A in growth is its role in promoting cellular differentiation. During embryonic development and throughout growing period, retinol is necessary for the proper differentiation of cells into specialized tissues and organs (Gudas and Wagner, 2011). In particular, vitamin A plays a crucial role in the growth and upkeep of epithelial tissues found in vital areas like the skin, respiratory system, urinary and digestive tract (Timoneda et al., 2018). These tissues act as a barrier against pathogens and environmental insults constituting an important part of the immune system (Jafari and Rohn, 2022). Furthermore, they are essential for nutrient absorption and gas exchange.

In addition to its role in cellular differentiation, vitamin A is also important for bone growth and development. Retinol deficiency in pigs and poultry has been shown to impair bone growth and increase the risk of bone malformations (Palludan, 1961; EFSA (European Food Safety Authority), 2013; Abd El-Wahab et al., 2017). This can be attributed, at least in part, to the role of vitamin A in promoting the production and activation of osteoblasts, which are the cells responsible for building new bone tissue (Chiba et al., 1996). Retinol is also involved in the regulation of bone resorption, which is the natural process of breaking down old bone tissue and replacing it with new bone tissue (Yee et al., 2021).

Finally, retinol is indispensable for reproductive health in birds and mammals (Lindemann et al., 2008; Chen et al., 2015). It is essential for the proper development and maintenance of reproductive organs, including the testes, ovaries, and uterus (Clagett-Dame and Knutson, 2011). Furthermore, retinoic acid is necessary for the differentiation of germ cells, which eventually give rise to eggs and sperm (Endo et al., 2019). Retinol also promotes the differentiation of Leydig cells, which produce testosterone in males, and theca cells, which produce estrogen in females (Yang et al., 2018).

Thus, vitamin A is a crucial micronutrient with diverse physiological functions, and its deficiency can cause health problems, emphasizing the importance of adequate intake.

3 The impact of vitamin A deficiency on immune function

Retinoids are recognized as one of the most crucial substances that exert a profound influence on the immune system of non-ruminant animals (Dalloul et al., 2002; Chattha et al., 2013; Hu et al., 2020; Amimo et al., 2022; Wan et al., 2022). They affect the differentiation, proliferation, and functionality of various immune cells, including T cells, B cells, natural killer (NK) cells, and dendritic cells (Oliveira et al., 2018). Retinoids regulate the expression of genes that are involved in immune function, including those controlling inflammation and cytokine production (Pino-Lagos et al., 2010). Insufficient vitamin A intake impairs immune cell function and modifies gene expression, resulting in reduced immune responses and increased susceptibility to infection in pigs and poultry (Ahmad et al., 2009; Pino-Lagos et al., 2010; Vlasova et al., 2013; Chepngeno et al., 2022; Zhang et al., 2023).

Green and Mellanby (1928) were the first to discover the role of vitamin A in immune modulation, which led to its recognition as "the anti-infective vitamin". Currently, retinol is one of the most investigated micronutrients regarding immune function (Villamor and Fawzi, 2005; Gürbüz and Aktac, 2022).

Vitamin A is crucial in maintaining the epithelial barrier, acting as the first line of defense against various infections (Huang et al., 2018). In instances of vitamin A deficiency, observed in the research conducted by Cortes et al. (2006), birds demonstrated clinical signs of squamous metaplasia and hyperkeratinization of glandular epithelium in numerous mucosal surfaces, including the esophagus, bursa of Fabricius, proventriculus, and nasal glands. Similar symptoms can be observed in different tissues of mammals experiencing hypovitaminosis A (Baldwin et al., 2012). However, the immunoregulatory effects of retinol go beyond its role in preserving the integrity of the epithelium and mucus layers.

According to Ahmad et al. (2009), insufficient vitamin A levels can significantly impact the immune system's antibody response. In particular, animals with low levels of this vitamin exhibit diminished IgM and IgG response, reduced production of specific IgM antibodies, and decreased salivary IgA antibody levels during infections (Stephensen, 2001; Hu et al., 2020 and Zhou et al., 2021). For instance, early studies by Harmon et al. (1963) found that pigs with vitamin A deficiency produced less than 10% of the antibody quantity compared to control pigs given vitamin A supplementation.

Vitamin A deficiency can have a significant impact on immune function, even before other symptoms become apparent. In fact, a seminal study by Friedman and Sklan (1989) using an avian model showed that vitamin A deficiency initially impairs serum antibody responses. However, this impairment can be rapidly reversed with the administration of retinyl acetate supplementation, highlighting the importance of early detection and intervention. Similar results were reported by Davis and Sell (1989) in broilers, where chicks fed a vitamin A-deficient diet showed significantly lower serum antibody responses to Newcastle disease virus (NDV) vaccination.

In viral infections, cell-mediated immune responses play an important role, and vitamin A deficiency can inhibit them. An investigation by Sijtsma et al. (1990) indicated that vitamin A deficiency decreased cytotoxic T lymphocyte activity against NDV-infected cells in chickens. As a result, the death of virus-infected cells may be delayed, increasing morbidity in birds infected with the virus.

In a more recent study, clinical signs of vitamin A deficiency in broiler chickens infected with NDV were observed, including greenish-white droppings, ruffled feathers, and leg weakness (Rizvi et al., 2003). Furthermore, vitamin A-deficient broilers showed a lower immune response to the virus, as demonstrated by a lower geometric mean titer compared to those with adequate vitamin A intake.

An array of endogenous retinoic acid metabolites has been shown to possess biological activity. Among them, 14-hydroxy-4,14-retro-retinol (14-HRR) and 3,14-di-OH-retinol are involved in the proliferation of T and B cells (Schuchardt, 2007). For example, 14-HRR is essential for the growth of B lymphocytes and activation of T lymphocytes (Carazo et al., 2021). Whether in insects or mammals, nearly every cell in the body has the capacity to convert all-trans retinol to 14-HRR, indicating the widespread conservation of this biochemical pathway (Blomhoff and Blomhoff, 2006). 14-HRR is structurally similar to retinoic acid, but with a hydroxyl group at position 14 and a reversed double bond at positions 4 and 14. In birds and animals, 14-HRR has been shown to enhance the proliferation of lymphocytes in response to mitogens as well as, it has been found to increase the production of cytokines by lymphocytes such as interferon-gamma, interleukin-2 or tumor necrosis factor (Mao et al., 2000).

Several studies have shown that subclinical vitamin A deficiency in animals can lead to immune dysfunction, compromising both innate and adaptive immune responses. Chattha et al. (2013) found that hypovitaminosis A in pigs impairs mucosal and systemic adaptive B and T lymphocyte responses as well as imbalances innate and adaptive cell distribution. Researchers reported that vitamin A deficient pigs had greater CD8 T cell frequencies in blood, spleen, duodenum, ileum, and lower frequencies of CD4 T cells in ileum after a challenge with a virulent rotavirus (RV; Figure 1). Further, plasmacytoid dendritic cells were found in significantly higher numbers in intestinal tissues and

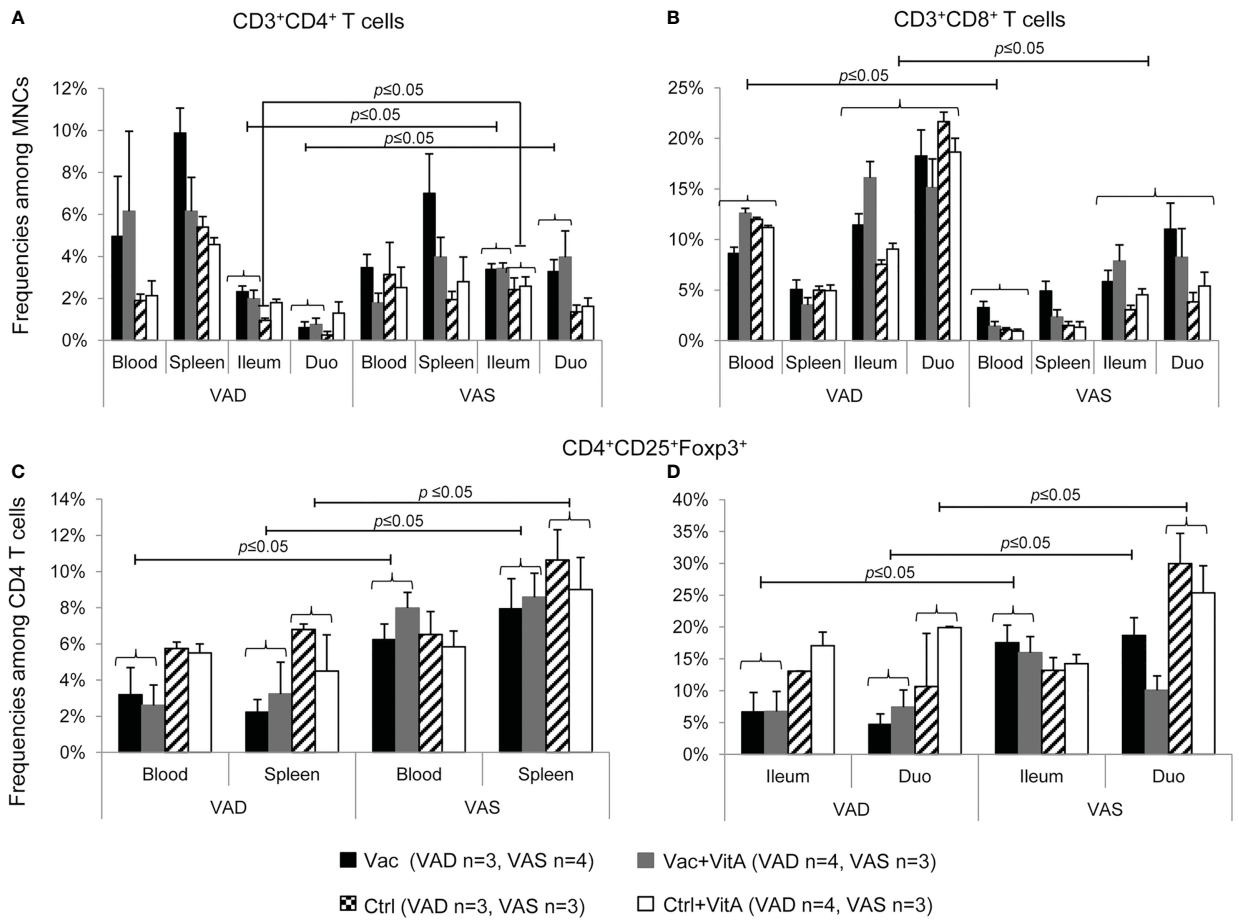

FIGURE 1
Following a human rotavirus (RV) challenge, the groups that were both vaccinated and had sufficient levels of vitamin A exhibited higher levels of intestinal and systemic T regulatory cells (Chattha et al., 2013). The graph compares frequencies of T helper cells (CD3+CD4+; **A**), cytotoxic T cells (CD3+CD8+; **B**) and regulatory T cells (CD4+CD25+Foxp3+; **C, D**) in vitamin A deficient and sufficient pigs; MNCs=mononuclear cells. Pigs were vaccinated with attenuated human RV (AttHRV) vaccine or given a placebo, with or without vitamin A supplementation. Data was collected from blood, spleen, ileum, and duodenum post-RV challenge. Bars show mean values and standard error of the mean, with capped lines indicating significant differences ($p \leq 0.05$). Labels: Vac=AttHRV vaccinated, Vac+VitA=AttHRV vaccinated + vitamin A, Ctrl=non-vaccinated/non-vit A pigs, Ctrl +VitA=vitamin A only; doi.org/10.1371/journal.pone.0082966.g005.

conventional dendritic cells in all tissues examined pre-challenge, suggesting dysregulation of overall immune responses in vitamin A-deficient swine. As well, low-vitamin A diets significantly reduced the CD4:CD8 T-cell ratios in chicken (Lessard et al., 1997).

In neonatal piglets, Kandasamy et al. (2014) examined the impact of vitamin A deficiency on the immune response to the rotavirus (RV) vaccine and subsequent infection. The results showed that vitamin A deficient piglets had compromised immune responses, higher fecal virus shedding, and lower protective efficacy against infection compared to vitamin A sufficient animals (100,000 IU at d 6, 16 and 28 of age). Vitamin A deficient piglets also had persistently elevated levels of pro-inflammatory mediator IL-8 and lower anti-inflammatory cytokine IL-10 responses, suggesting more severe inflammatory reactions. The study concluded that vitamin A deficiency impairs the immune response to the rotavirus vaccine and reduces vaccine efficacy against infection. Oral vitamin A supplementation concurrent with the vaccine did not improve vaccine efficacy in vitamin A deficient piglets. Thus, the studies of Lessard et al. (1997); Chattha et al. (2013) and Kandasamy et al. (2014) demonstrate the important role of vitamin A in maintaining a balanced and functional immune system in animals, as its deficiency can lead to dysregulation of innate and adaptive immune responses.

In chicks, Davis and Sell (1983) demonstrated that vitamin A deficiency impaired lymphocyte proliferation in response to mitogenic stimulation and reduced the growth of the bursa of Fabricius and thymus, both of which are crucial in the development and maturation of different types of white blood cells (e.g., lymphocytes) that are essential for proper immune system function (Schat, 2022).

Dalloul et al. (2002) conducted a study to investigate the impact of vitamin A deficiency on the intestinal immune response and disease susceptibility to coccidiosis in broiler chickens infected with *Eimeria acervulina*. The researchers found that birds fed a vitamin A-deficient diet had fewer intraepithelial lymphocytes expressing surface markers CD3, CD4, CD8, αβTCR, and γβTCR, regardless of whether they were challenged with *Eimeria* or not. Moreover, the vitamin A-deficient birds shed significantly more *Eimeria* oocysts and produced lower levels of interferon-γ than birds on a vitamin A-supplemented diet,

indicating that vitamin A deficiency can compromise local immune defenses and increase disease susceptibility in broiler chickens.

Vitamin A is known to be essential for maintaining the integrity of various systems in the body, including the gastrointestinal tract. In a study by Idi et al. (2007), the effect of vitamin A deficiency on chickens infected with *Ascaridia galli* eggs was investigated. The results indicated that vitamin A plays a crucial role in moderating *A. galli* infection in poultry.

The impact of hypovitaminosis A on respiratory infections in young animals is well established. To address this issue, McGill et al. (2019) recently carried out an investigation on bovine respiratory syncytial virus (BRSV), a pathogen that causes lower respiratory tract disease. The researchers developed a nanovaccine that contained BRSV proteins encapsulated in polyanhydride nanoparticles. However, when tested on calves with vitamin A deficiency, the vaccine did not produce the desired response, and the animals were not protected from BRSV challenge. Interestingly, the study also revealed that acute BRSV infection had a negative effect on both serum and liver retinol levels. These results underscore the crucial role of vitamin A in regulating respiratory mucosa immunity in animals. The calf model used in the study proved to be a valuable tool for investigating the impact of nutritional status on mucosal immunity and viral infections.

Romagnani (1999) note that Type 1 T helper (Th1) cells generate interferon-gamma, interleukin-2, and tumor necrosis factor-beta, which activate macrophages and facilitate cell-mediated immunity and phagocyte-dependent protective responses. On the other hand, type 2 Th (Th2) cells produce IL-4, IL-5, IL-10, and IL-13, promoting robust antibody production, eosinophil activation, and the inhibition of various macrophage functions, thereby providing phagocyte-independent protective responses. Th1 cells generally emerge after infections caused by intracellular bacteria and some viruses, while Th2 cells are more prevalent in response to infestations caused by gastrointestinal nematodes.

Cantorna et al. (1994) discovered that vitamin A has at least three important functions that help to balance Th1 and Th2 activities. These functions include directly down-regulating the secretion of interferon-gamma by Th1 cells, reducing the function of activated antigen presenting cells, and promoting the growth and/or differentiation of Th2 cells. The antigen-presenting cells play a central role in vitamin A's immune system functions (Duriancik et al., 2010). This imbalance between regulatory Th1 and Th2 cells is believed to be a contributing factor to poor antibody-mediated immunity in cases of hypovitaminosis A.

Amimo et al. (2022) observed that, generally, there is a tri-directional relationship between vitamin A deficiency, immune response, and infections. Vitamin A deficiency affects the immune system and makes it more susceptible to infection, and infection decreases the absorption of vitamin A, resulting in secondary retinol deficiency in animals.

Hence, it is acknowledged that retinol and its metabolites are important substances for immune function, as studies have revealed that vitamin A deficiency can considerably affect the immune system's antibody response and impair the proliferation and function of immune cells.

In conclusion, it is important to make some critical remarks. Although the overwhelming majority of research suggest that inadequate vitamin A intake can impair immune system function, the optimal level of vitamin A required for maintaining immune health remains unclear. Furthermore, excessive intake of vitamin A can lead to hypervitaminosis A, which may cause certain adverse effects. Thus, it is essential to strike a balance in the recommended vitamin A intake level for immune health to avoid potential negative consequences.

4 The immunomodulatory effects of vitamin A supplementation

Supplementation of vitamin A in diets of non-ruminants has been used as a strategy to enhance immunity and health. However, several immunomodulatory effects of supplemental vitamin A on different aspects of the immune system in pigs and poultry are still a matter of debate and require further investigation.

4.1 Research in swine

It is known that RV is the main pathogen responsible for severe diarrhea in young animals that causes dehydration (Chang et al., 2012). Chepngeno et al. (2022) found that vaccinating pregnant sows with RV (maternal immunization) led to increased lactogenic immunity and passive protection in their piglets, and that vitamin A supplementation (daily oral retinyl palmitate at 30,000 IU) during gestation and lactation enhanced sow immune responses and passive protection of their offspring. Furthermore, RV challenge caused severe diarrhea and higher shedding of viral RNA in retinol deficient (no vitamin A supplementation was provided to the mother) mock-inoculated piglets than in vaccinated or vitamin A sufficient piglets (Table 1). These findings shed light on the immunomodulatory effects of retinol during infection/vaccination, the impact of maternal vitamin A deficiency and immunization on neonatal passive immune protection and have important implications for improving vaccination programs for swine RV, which may lead to better control of RV infection in neonates.

Langel et al. (2019) used a pregnant swine model to study the effects of vitamin A supplementation on porcine epidemic diarrhea virus (PEDV)-infected gilts. They found that vitamin A supplementation in the third trimester (daily oral retinyl acetate at 30 000 IU) improved gut homeostasis and immune regulation, and increased anti-PEDV IgA immunity in the blood, milk, and ileum. This translated to improved survival rates in PEDV-challenged litters. The study suggests that vitamin A supplementation may enhance intestinal immunity during pregnancy and lactation and inform maternal vaccination and retinol supplementation strategies for enteric viral diseases in humans and animals.

According to Vlasova et al. (2013), even marginal (subclinical) vitamin A deficiency can compromise innate and adaptive immune responses, rendering individuals more vulnerable to infections. In piglets infected with RV, vitamin A deficiency resulted in prolonged fecal shedding of the virus, higher titers of the virus, and more severe diarrhea compared to piglets that received vitamin A supplementation. The authors suggest that early (shortly prior to vaccination or virulent RV exposure) and sustained vitamin A supplementation for both

TABLE 1 Piglet diarrhea and RV* RNA peak shedding data (Chepngeno et al., 2022).

Piglet Groups	No. of Piglets	Average peak RV RNA Titer (Log 10 GE/mL)	% of pigs with **diarrhea (Score = ≥2)	Mean No. of Days to Onset of Diarrhea	***Mean Cumulative Fecal Score
VAD + RV	52	7.1^{ab}	5.1	2	1.6^{b}
VAD-Mock	26	15.0^{a}	36.8	2	4.8^{a}
VAD + VA + RV	52	4.1^{b}	7	2	1.4^{b}
VAD + VA-Mock	27	9.6^{ab}	18.5	2	2.8^{c}
VAS + RV	20	4.1^{b}	0	2	1.1^{b}
VAS-Mock	17	7.5^{ab}	23	2	2.5^{c}

*RV=Rotavirus; VA=Vitamin A; VAD=Vitamin A deficient diet; VAS=Vitamin A sufficient diet; **Diarrhea is defined as fecal score ≥2. Fecal diarrhea was scored as follows: 0, normal; 1, pasty; 2, semiliquid; 3, liquid. ***Mean cumulative fecal score [sum of fecal consistency score days post inoculation (Post Challenge Day 0-12)/N], where N is the number of pigs receiving the inoculation. $^{a\text{-}c}$represents significant differences among the groups within the column ($p \leq 0.05$). ^{ab}represents no significant differences to any group within the column.
doi.org/10.3390/v14112354.

mothers and their offspring may help maintain intestinal health and restore normal immune response in swine. However, further research is needed to determine the optimal timing, dosage, and duration of vitamin A supplementation for swine infected with RV and to assess its long-term effects on their health and immune system.

As per available data, *Ascaris suum*, also known as the large roundworm of pigs, infects over 50% of fattening swine worldwide in meat production systems (Zheng et al., 2020). However, animal trials have revealed that vitamin A supplementation (>100 µg of retinoic acid per kg of body weight) can bolster the localized immune response in parasitic nematode-infected growing swine. In a study by Dawson et al. (2009), vitamin A supplementation (as retinoic acid) was found to increase the expression of markers for T lymphocytes (Th1, Th2, and regulatory T cells) in the liver and lungs, as well as elevate lung eosinophilia in the large roundworm-infected pigs (Figure 2). While both supplementation levels of vitamin A (100 and 1000 µg per kg of body weight) resulted in a significant improvement compared to the control group (without vitamin A supplementation), there was no statistically significant difference observed between the low and high doses. This suggests that the response, specifically lung eosinophilia, was maximized at the lowest level of vitamin A provision. Based on their findings, the researchers concluded that vitamin A supplementation can trigger a robust immune response that is effective in controlling parasites and reducing inflammation. Nonetheless, it is recommended to conduct additional research on the efficacy of vitamin A in parasitic nematode-infected pigs across various production systems and geographical regions. Further investigation will help to better understand the potential benefits of vitamin A in these contexts.

Hu et al. (2020) and Zhou et al. (2021) conducted studies to assess the effects of various sources of vitamin A on growth performance, immune status, and antioxidant capacity in weaned piglets. Both studies demonstrated that supplementing vitamin A (at 12,000 or 13,500 IU/kg feed) can significantly improve ($P < 0.05$) the levels of immunoglobulins (IgM, IgA, IgG) in blood serum compared to the non-supplemented group (0 IU/kg feed). Vitamin A is known to be vital for the production of anti-viral substances, including lysozyme (West et al., 1991). In line with this, the study conducted by Zhou et al. (2021) found that supplementing vitamin A significantly increased the level of lysozyme in the blood serum of post-weaned piglets.

The notable study conducted by Sole et al. (2022) provides insight into the potential immunomodulatory effects of vitamin A supplementation in pigs with a specific genetic haplotype. The

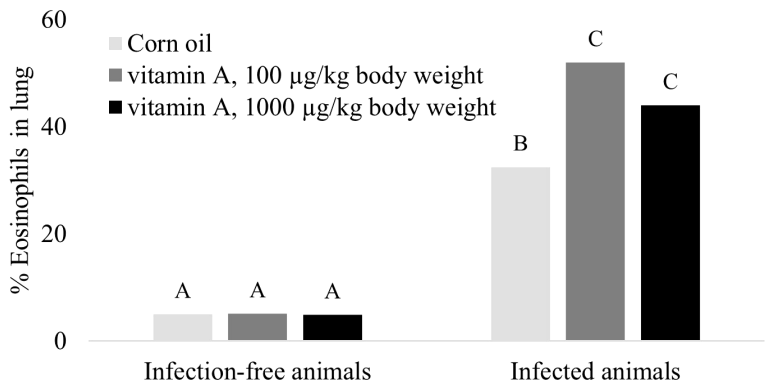

FIGURE 2
Treatment of pigs with vitamin A increased eosinophils in lung tissue after inoculation with the large roundworm (adapted from Dawson et al., 2009). Treatments annotated with unique letters (A–C) are statistically different ($P < 0.05$). doi: 10.1128/IAI.00827-07.

findings suggest that vitamin A supplementation not only induces alterations in fatty acid desaturation, but also stimulates several metabolic and signaling pathways associated with immunity, inflammation, and fat metabolism. These results provide further evidence for the potential of vitamin A to enhance immune function and alleviate inflammation in this specific population of pigs.

4.2 Research in poultry

Similarly to swine, supplemental vitamin A has been found to exert immunomodulatory effects on both innate and adaptive immune responses in domestic fowl.

According to a study by Lin et al. (2002), even though the liver of laying hens exposed to heat stress (31.5°C) and vaccinated against NDV contained high levels of stored vitamin A, the increased amount of dietary retinol (12,000 IU per kg of feed) had a significant and positive impact on the counts of T-lymphocytes in peripheral blood. Riabroy and Tanumihardjo (2014) mention that because retinol is rapidly taken up by tissues and tends to return to its baseline levels in all tissue types except for the liver, where it is stored for the long term, it is necessary to maintain a steady dietary intake to ensure sufficient vitamin A levels in immune organs. Additionally, supplementation of vitamin A (75 mg of retinol/kg body weight/day) boosted phagocytic activity and reactive oxygen production by Kupffer cells and monocytes in animals with adequate vitamin A levels (Hoglen et al., 1997). Moreover, research in adult animals suggests that higher whole body vitamin A stores are linked to increased numbers of NK cells and NK T cells in the peripheral blood (Ahmad et al., 2009). Thus, ensuring an adequate quantity of supplemental retinol is essential for building up sufficient body reserves in both swine and poultry.

A recent research by Zhang et al. (2023) found that oral vitamin A supplementation (8,000 IU per kg diet) improved the immune response of White Leghorn chickens infected with infectious bronchitis virus (IBV). The chickens were treated daily until 21 days old, and then infected with a pathogenic IBV strain. Vitamin A lowered viral replication and increased serum IgG levels, while reducing the inflammatory response. Although clinical course of disease and growth performance were not affected, these findings highlight vitamin A's crucial role in regulating chicken-IBV interactions and innate immunity.

Similar observations related to vitamin A and immunity have been made in other studies, where supplementing vitamin A in broilers improved the immune response of NDV-vaccinated birds, as indicated by an increase in haemagglutination inhibition titres, suggesting that sufficient vitamin A intake may enhance the effectiveness of NDV vaccination in poultry production (Sanda and Oyewole, 2015).

Testing different levels of vitamin A for immune response function is essential for understanding the role of retinol in supporting the immune system, identifying the optimal range of vitamin A supplementation, and developing evidence-based recommendations to optimize bird health and welfare in poultry production.

Lessard et al. (1997) reported that providing broiler breeders with vitamin A supplementation ranging from 1,500 IU/kg to 15,000 IU/kg of feed significantly boosted their NDV virus antibody titers. As well, Yuan et al. (2014) showed that increasing vitamin A supplementation from 5,000 IU/kg to 20,000 IU/kg of feed increased NDV antibody titer in broiler breeders, but a further increase from 20,000 to 35,000 IU/kg led to a decrease in this parameter (Table 2). The bell-shaped response suggests that it is pivotal to determine the optimal range of vitamin A supplementation for different species and stages of growth to achieve maximum health benefits.

In a study by Sklan et al. (1994), the impact of dietary vitamin A on antibody production and T cell proliferative response in broiler chickens aged 21 to 39 days was investigated in response to ß-casein or *Mycobacterium tuberculosis*. The experimental diets were supplemented with vitamin A at various levels from hatching.

TABLE 2 Effect of dietary vitamin A on antibody response to NDV in broiler breeders* (Yuan et al., 2014).

Treatment/vitamin A	Week 4**	Week 8	Week 12	Week 16	Week 20
A (5,000 IU/kg)	9.8	8.3	6.3^{a}	9.3^{b}	6.8
B (10,000 IU/kg)	8.8	7.6	7.0^{a}	8.0^{ab}	7.2
C (15,000 IU/kg)	9.8	7.0	6.7^{a}	8.3^{ab}	7.4
D (20,000 IU/kg)	9.2	6.8	8.3^{bc}	6.8^{a}	7.2
E (25,000 IU/kg)	9.4	7.2	8.8^{c}	6.6^{a}	7.6
F (30,000 IU/kg)	8.8	7.4	7.3^{ab}	6.8^{a}	7.8
G (35,000 IU/kg)	9.6	6.8	6.8^{a}	7.4^{a}	8.0
SEM	0.14	0.19	0.22	0.23	0.14
p-value					
Combined	0.195	0.478	0.003	0.012	0.282
Linear	0.143	0.660	0.002	0.142	0.975
Quadratic	0.108	0.731	0.044	0.603	0.936

*NDV=Newcastle disease virus; The titers were expressed as log2 of the highest dilution based on total agglutination; **36-week-old Ross-308 broiler breeder hens fed experimental diets for 20 weeks; Week 4 = Period 1 (birds aged 36-40 weeks); Week 8=Period 2 (birds aged 40-44 weeks); Week 12=Period 3 (birds aged 44-48 weeks); Week 16=Period 4 (birds aged 48-52 weeks); Week 20=Period 5 (birds aged 52-56 weeks). $^{a-c}$Within a column, values not sharing a common superscript letter are significantly different ($p<0.05$).
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Results showed that optimal immune responses were achieved at a dietary intake of 6,660 μg/kg (ca. 20,000 IU/kg), beyond which the responses decreased, while optimal growth required only about 5,000 IU/kg. These findings suggest that higher levels of vitamin A supplementation than the National Research Council (NRC) (1994) recommendations may be needed for best immune function in broiler chickens. In a subsequent trial by Sklan et al. (1995), turkey poults aged 21 to 41 days were fed diets with varying levels of vitamin A supplementation from 0 to 13,200 μg/kg feed, and antibody production and T-cell proliferative response were measured against immunization with NDV and turkey pox vaccines. Similar to the broiler trial, increasing dietary concentrations of vitamin A enhanced the proliferative response until the diet contained 6.0 μg/g (ca. 18,000 IU/kg), above which the response began to decrease. The study also found a clear difference in vitamin A requirement for optimal body weight and immune response, with higher levels required for the latter parameter.

In their study, Guo et al. (2019) investigated the impact of dietary vitamin A levels on broiler growth performance and immune parameters. For 42 days, broilers were fed with different vitamin A levels ranging from 3,000 to 45,000 IU/kg. The researchers found that varying dietary vitamin A levels significantly influenced broiler growth performance and serum immune factors, including interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). Interestingly, the 3,000, 6,000, and 45,000 IU/kg groups exhibited lower levels of serum immune factors, whereas the 15,000 IU/kg group showed higher levels. Guo et al. (2019) concluded that broiler diets supplemented with vitamin A at 6,000 and 15,000 IU/kg could enhance weight gain and immune response. However, higher vitamin A levels (30,000 and 45,000 IU/kg) may lead to reduced growth performance and immunological parameters in broilers.

Sepehri Moghaddam and Emadi (2014) aimed to assess the effect of vitamin A on the immune system of broilers. The experiment included four diets with varying levels of vitamin A (0, 1500, 6250 and 11000 IU/kg feed), and the immunological response was evaluated using several measures such as immunoglobulin titers, cutaneous basophil hypersensitivity, and heterophils and lymphocytes counts. The findings demonstrated that higher vitamin A supplementation significantly increased immunoglobulin titers and cutaneous basophil hypersensitivity in broilers. This suggests that the latest vitamin A requirement of 1,500 IU/kg feed recommended by National Research Council (NRC) (1994) for broilers might not be sufficient to fulfill the requirements of the current high performing broiler strains. Therefore, the study emphasizes the importance of revising the vitamin A recommendations for broilers to improve their immune response and overall health. Similar results were reported Faluyi and Agbede (2017) as in their study higher vitamin A supplementation (100 or 200 mg/kg) led to highest antibody titres.

Li et al. (2022) investigated the effects of vitamin A on the immune function of aged laying hens. The researchers formulated diets with deficient (0 IU/kg), adequate (7000 IU/kg), and excess levels (14,000 IU/kg feed) of vitamin A and fed them to 87 weeks old laying hens for eight weeks. The results showed that hens fed with adequate or excess levels of vitamin A had higher plasma immunoglobulin G content and mRNA expression of interleukin-10 in the spleen. They also had lower mRNA expression of IL-1β in the jejunum and iNOS and TNF-α in the spleen.

Despite prior research suggesting a possible connection between the administration of vitamin A supplements and the immune response in poultry, a study conducted by Coskun et al. (1998) found no significant impact on the immune response of laying hens. Specifically, the authors reported that dietary supplementation with up to 24,000 IU/kg of vitamin A had no significant effect on the levels of T lymphocytes in the peripheral blood, plasma cell counts in the spleen, or antibody titers against NDV in Hisex-brown laying hens. This research stands in contrast to earlier studies that demonstrated a potential relationship between vitamin A supplementation and immune response in chickens.

Geese are important in poultry production due to their high-value products, adaptability to different environments and production systems, proficiency to produce for several years, foraging ability, and cultural significance. In a 28-day study, goslings were fed diets with different levels of vitamin A (0, 3,000, 6,000, 9,000, 12,000, and 15,000 IU/kg feed) to evaluate the impact on intestinal morphology and immune response (Zhang et al., 2022). Increasing levels of vitamin A resulted in higher villus height and width, crypt depth, and muscular layer thickness in the duodenum, jejunum, and ileum ($P < 0.05$). Higher serum immunoglobulin A and G levels were also observed with increased vitamin A intake ($P < 0.05$). In addition, levels of interleukin-1 and interleukin-6 were higher in some groups, while interleukin-2 levels were higher in one group, all compared to the group without vitamin A supplementation ($P < 0.05$). This data suggest that dietary vitamin A levels have a significant impact on the intestinal morphology and immune response of various domestic fowl species.

Overall, the results of the dose-response studies indicate that the impact of dietary vitamin A on immune response in poultry may vary depending on factors such as the type of bird, specie, age, and dosage.

Monitoring vitamin A levels in both mother and offspring can help to identify and address any deficiencies or imbalances that could negatively impact maternal and progeny vitality.

Wang et al. (2020) demonstrated that vitamin A supplementation at both the maternal and offspring levels had a positive impact on immune function in broilers. Specifically, a diet high in retinol was associated with enhanced growth performance and an increased relative bursa of Fabricius ratio. A bird's immune health is reflected in its immune organ ratio. Vitamin A appears to be particularly important for immune organ development in the starter phase (Wang et al., 2020).

In their 2020 study, Yang et al., (2020) investigated the impact of maternal and offspring dietary vitamin A supplementation on the performance, digestive tract function, and immune function of goslings. The researchers administered varying doses of vitamin A to the maternal (0, 4,000, 8,000, 12,000, or 16,000 IU/kg) and offspring (0 or 9,000 IU/kg) diets. The results revealed that supplementing the maternal geese's diet with 12,000 IU/kg vitamin A led to a significant increase in immune organ weight, immune organ index, and immunoglobulin content in goslings ($P < 0.05$). Furthermore, the offspring of the 9,000 IU/kg vitamin A supplementation group exhibited higher bursa weight and

immunoglobulin G content than those in the group with no supplementation ($P < 0.05$). The study also found that maternal vitamin A deficiency had a negative impact on offspring, but this effect was counteracted by adding vitamin A to the offspring's diet. However, prolonged vitamin A supplementation in the offspring's diet after excessive vitamin A supplementation in the maternal diet was found to be detrimental to gosling growth and development.

4.3 Research *in ovo*

In ovo research is important for investigating the effects of varying levels of vitamin A on embryonic development and the resulting consequences on health outcomes, providing a cost-effective and ethical alternative to traditional animal models while informing strategies for optimizing maternal and fetal vitamin A status to support healthy development and prevent long-term health consequences.

Shojadoost et al. (2021) demonstrated the positive effects of *in ovo* injection of vitamin A (retinoic acid at 30, 90, and 270 µmol/egg *via* the amniotic sac) on the immune system of chicken embryos. The results showed that higher doses of vitamin A had an anti-inflammatory effect, reducing the expression of certain genes in the spleen after 24 hours. This suggests that vitamin A can effectively modulate the immune functions of chicken embryos, potentially enhancing immune responses to *in ovo* vaccines. Similarly, Alizadeh et al. (2022) found that giving neonatal chickens retinoic acid at a dose of 90 mmol/egg during embryonic day 18 improved their immune response. The birds were immunized with two T-dependent antigens, on post-hatch days 14 and 21. Retinoic acid significantly increased serum IgY and IgM titers and stimulated the expression of various cytokines, including IFN-a, IL-1b, IL-6, IL-8, IL-12, IL-13, and TGF-b ($P < 0.05$). Additionally, retinoic acid increased the percentage of CD3+CD8+ T cells and KUL01+ monocyte/macrophages in the spleen ($P < 0.05$). Thus, administering retinoic acid before hatching enhances the chicken's immune system by increasing cytokine production that regulates innate immunity and improving the antibody-mediated response to T-dependent antigens. Still, further studies are needed to investigate the long-term effects of *in ovo* or neonatal administration of vitamin A on the immune system of poultry, as well as its potential impact on the safety and efficacy of *in ovo* vaccination programs.

In conclusion, additional research is necessary to determine the optimal timing, dosage, and duration of vitamin A supplementation for swine and poultry infected with various pathogens, and to assess its long-term effects on their health and immune system. Testing different levels of vitamin A for immune response function is essential for identifying the optimal range of vitamin A supplementation and developing evidence-based recommendations to optimize animal health and welfare in production systems.

5 Effect of hypervitaminosis A on immune function

Hypervitaminosis A is a condition that can be induced when animals, including swine and poultry, consume excessive amounts of retinol. Although vitamin A is indispensable for proper nutrition, it is crucial to maintain a balanced intake to avoid adverse effects.

The susceptibility to hypervitaminosis A in animals can be influenced by several factors, including breed, age, the level of vitamin A dosage, the form of vitamin used, the route and frequency of its administration, as well as factors involved in the absorption of fat-soluble vitamins (Sideeg, 1996).

When birds and mammals are exposed to excessively high levels of vitamin A, it can potentially have detrimental effects on their immune function. A study conducted by Yuan et al. (2014) demonstrated this by investigating the effects of different vitamin A supplementation levels on broiler breeders. Increasing vitamin A supplementation from 5,000 IU/kg to 20,000 IU/kg of feed resulted in an increase in NDV antibody titer. However, a further increase to 35,000 IU/kg led to a decrease in this parameter. In contrast, Coskun et al. (1998) reported no significant effects of dietary supplementation with vitamin A at levels up to 24,000 IU/kg on the immune response of Hisex-brown laying hens. According to their findings, there were no notable changes in the levels of T lymphocytes in the peripheral blood, plasma cell counts in the spleen, or antibody titers against NDV in response to the supplementation.

Sklan et al. (1994) and Sklan et al. (1995) conducted studies to investigate the effect of increasing doses of vitamin A, up to 44,000 IU/kg feed, on the growth and antibody production in broiler chickens and turkeys. The results of their research showed that both antibody production and T cell proliferative response reached a plateau at approximately 20,000 IU of vitamin A supplementation. However, at the highest supplementation level of 44,000 IU/kg feed, there was a reduction in these parameters, indicating a bell-shaped response. Guo et al. (2019) reported similar findings in a more recent study in broilers.

Swine seem to be much more tolerant to higher supplementation levels of retinol compared to poultry. For instance, a study conducted on piglets weighing 8 kg initially and up to 90 kg investigated the effects of feeding very high doses of vitamin A, reaching up to 220,000 IU/kg of feed (Blair et al., 1992). The researchers found no clinical signs of toxicity and observed no adverse effects on bone health. However, they did note an increase in plasma and liver levels of vitamin A as a result of the supplementation.

Recent studies have indicated that high intake of vitamin A can result in the development of resistance to hypervitaminosis A. In a study by Bozhkov et al. (2021), experimental animals were administered vitamin A daily at a dose of 300 IU/100 g of body weight. It was observed that vitamin A accumulated in the liver, reaching a concentration of 250-300 mg/g. Surprisingly, subsequent administrations of vitamin A led to a decrease in its content in the liver, suggesting the presence of a potential resistance mechanism.

Additional research, such as the study by Arts et al. (2015), has indicated that hypervitaminosis A in mammals could compromise the immune response, rendering them more susceptible to infections and diseases. It is believed that excessive vitamin A can disrupt the balance and activation of immune cells, thus interfering with the intricate network of immune responses. This notion is

supported by studies conducted on rats, where the administration of vitamin A significantly higher than their dietary requirements (8,000 and 15,000 IU/kg body weight) had a stimulatory effect on total white blood cell and neutrophil counts, while inhibiting basophil and total lymphocyte counts (Mahassni and Al-Shaikh, 2013).

Moreover, excessive intake of vitamin A can have an impact on the production of antibodies, which play a crucial role in recognizing and targeting specific pathogens. This can potentially compromise the ability of swine and poultry to effectively combat infections and maintain optimal immune responses. In a study conducted on viral pneumonia interventions (Cui et al., 2000), animals that were fed a very high level of vitamin A (250,000 IU/kg diet) demonstrated greater salivary immunoglobulin IgA responses compared to the control group (4,000 IU/kg diet). Conversely, the control group exhibited significantly higher serum IgG responses compared to the high-level group (P = 0.028). Additionally, the production of interferon-gamma (IFN-gamma), a Th1 cytokine, was found to be lower in the high-level diet group.

It is important to note that the negative effects of hypervitaminosis A on immune function in swine and poultry are typically observed when animals are exposed to extremely high levels of the vitamin for extended periods. It is extremely rare for such excessive intake to occur under normal feeding conditions (EFSA (European Food Safety Authority), 2008). Therefore, proper nutritional management and regular monitoring of vitamin A levels in animal diets are essential to prevent the development of hypervitaminosis A and maintain optimal immune function.

6 The potential applications of vitamin A as an immuno-micronutrient for improving health and preventing diseases

Vitamin A has emerged as a promising immuno-micronutrient for optimizing health and disease prevention in pig and poultry production (Alagawany et al., 2020; Lauridsen et al., 2021). The above-mentioned studies have demonstrated that vitamin A supplementation can effectively enhance the immune response and reduce the incidence and severity of infectious diseases in non-ruminants. However, it is important to note that further research is needed to fully understand the optimal dosage and potential interactions with other nutrients in order to maximize the benefits of vitamin A supplementation in non-ruminant production.

There are various ways how to administer vitamin A to pigs and domestic fowl:

1. Feed supplementation: retinol (usually as retinyl acetate) can be added to the diet in the form of a premix or a mineral feed.
2. Injection: retinol (usually as retinyl propionate or sometimes as retinyl palmitate) can be administered via injection to individual animals, either intramuscularly or subcutaneously.
3. Oral application: retinol (usually as retinyl palmitate) can be administered orally to individual animals.
4. Water supplementation: retinol (usually as retinyl acetate or retinyl palmitate) can also be added to the drinking water by using special water-dispersible formulations or vitamin mixes.

Yet, it is always important to take into account the local regulatory requirements and conditions of use for retinyl esters. For example, in the European Union, the use of vitamin A in water must adhere to specific guidelines. The concentration of vitamin A in water, when combined with the amount of vitamin A already present in the feed, must not exceed the recommended intake levels for certain species/categories (EFSA (European Food Safety Authority), 2013). These intake levels are determined based on the maximum content of vitamin A that is authorized for use in feed. EFSA (European Food Safety Authority) (2013) proposes the following maximum contents for vitamin A in complete feeds:

Pigs: piglets (weaned or suckling) 16 000 IU/kg complete feed; pigs for fattening 6 500 IU/kg complete feed; sows: 12 000 IU/kg complete feed.

Poultry: chickens (including all minor poultry species) in the first 14 days of life and turkeys in the first 28 days of life 20 000 IU/kg complete feed; all poultry (for fattening, reared for laying, laying and breeding) 10 000 IU/kg complete feed.

When determining the vitamin A requirements for pigs and poultry, it is crucial to consider the type of administration, the animal's age, and production stage. The type of vitamin A administration can affect the bioavailability and absorption of vitamin A, which in turn can impact the animal's overall vitamin A status and requirements. Young animals generally have higher vitamin A needs than mature animals, as they require vitamin A for growth and development (McDowell, 2000). Moreover, the necessary level of vitamin A may vary based on the purpose, with higher amounts required for maintaining a healthy immune system compared to performance or reproduction (McDowell, 2006). Generally, a factorial approach is indispensable in determining the precise vitamin A requirements as it considers a range of factors that influence the animal's vitamin A needs, such as age, sex, physiological status, and other dietary factors.

A healthy immune system is critical for swine and poultry production because it helps prevent and control infectious diseases, which can lead to reduced productivity, increased mortality, and economic losses for farmers and integrators (Lauridsen, 2019; Raja Kumari Kallam and Sejian, 2021). Infectious diseases can spread quickly in animal populations, and in severe cases, can cause significant damage to the entire herd or flock (Machalaba et al., 2015). A strong immune system also helps animals better cope with environmental stressors, such as changes in temperature, nutrition, or vaccination (Scarola et al., 2019). In addition to its role in preventing and controlling infectious diseases, a healthy immune system also contributes to overall animal health and well-being. Animals with a strong immune system are more likely to grow and develop optimally, have better reproductive performance, and have lower incidences of other health problems (Doeschl-Wilson et al., 2009). Retinol, with its well-earned nickname "the anti-infective vitamin", can be considered a pivotal vitamin in immune modulation among all vitamins. Therefore,

maintaining a healthy immune system is critical for non-ruminant production, and farmers must take appropriate measures to ensure that their animals receive the right amount of vitamin A, correct dietary levels of other nutrients, appropriate vaccination, and management practices to support optimal immune function. In general, vitamin A requirements are affected by a variety of environmental, genetic, and nutritional factors, highlighting the need for a comprehensive approach when determining vitamin A needs (Chen et al., 2015).

Failure to address immune system health in non-ruminant production can result in devastating consequences not only for animal welfare but also for public health, as infectious diseases in animal populations can also pose a threat to human health through zoonotic transmission. Therefore, it is imperative that farmers and integrators prioritize immune system health as a critical component of their management practices to ensure both the well-being of their animals and the safety of the public.

Overall, the potential applications of vitamin A as an immuno-micronutrient for improving health and preventing diseases in pigs and poultry are promising. However, further research is needed to determine the optimal dosage and timing of retinol supplementation/administration for different stages of growth and production systems, as well as its potential interactions with other nutrients and feed ingredients. Nonetheless, in the practical usage of vitamin A, the respective local legal regulations must be considered and therefore any application must always be carried out within the framework of the legal provisions.

7 Conclusion

Based on this scientific review, the following conclusions and recommendations can be drawn:

Firstly, vitamin A is essential for various physiological processes, including vision, growth, and immunity. It is primarily obtained from dietary sources and is metabolized into its active form, retinoic acid, which regulates gene expression and immune function.

Secondly, vitamin A deficiency can impair immune function in non-ruminants, leading to increased susceptibility to infections, reduced vaccine efficacy, and compromised gut health. Hypovitaminosis A also affects the integrity of mucosal barriers and can lead to inflammation and oxidative stress.

Thirdly, retinol plays a crucial role in regulating both innate and adaptive immune responses. It enhances the activity of immune cells, such as T cells, B cells, and NK cells, and promotes the production of cytokines, antibodies, and immunoglobulins. Vitamin A also regulates gut-associated lymphoid tissue and maintains the integrity of the gut barrier.

Lastly, supplementation with vitamin A has been shown to improve growth, immune function, and disease resistance in swine and poultry. It can enhance the immune response to vaccines, reduce the incidence of parasitic, respiratory and enteric diseases, and improve the quality of meat and eggs.

Based on these findings, it is recommended that non-ruminant diets are formulated to meet the vitamin A requirements to ensure optimal immune function and disease resistance. Additionally, higher supplementation/administration with vitamin A may be beneficial in situations where animals are at risk of deficiency, such as during periods of stress or disease challenge. Further research is needed to optimize the use of vitamin A as an immuno-micronutrient and to explore its potential as a tool for improving animal health and welfare.

Author contributions

YS wrote the manuscript and WP edited, reviewed, and approved the manuscript for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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