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Interplay of poultry–microbiome interactions – influencing factors and microbes in poultry infections and metabolic disorders

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ABSTRACT

1. The poultry microbiome and its stability at every point in time, either free range or reared under different farming systems, is affected by several environmental and innate factors. The interaction of the poultry birds with their microbiome, as well as several inherent and extraneous factors contribute to the microbiome dynamics. A poor understanding of this could worsen poultry heath and result in disease/metabolic disorders.
2. Many diseased states associated with poultry have been linked to dysbiosis state, where the microbiome experiences some perturbation. Dysbiosis itself is too often downplayed; however, it is considered a disease which could lead to more serious conditions in poultry. The management of interconnected factors by conventional and emerging technologies (sequencing, nanotechnology, robotics, 3D mini-guts) could prove to be indispensable in ensuring poultry health and welfare.
3. Findings showed that high-throughput technological advancements enhanced scientific insights into emerging trends surrounding the poultry gut microbiome and ecosystem, the dysbiotic condition, and the dynamic roles of intrinsic and exogenous factors in determining poultry health. Yet, a combination of conventional, -omics based and other techniques further enhance characterisation of key poultry microbiome actors, their mechanisms of action, and roles in maintaining gut homoeostasis and health, in a bid to avert metabolic disorders and infections.
4. In conclusion, there is an important interplay of innate, environmental, abiotic and biotic factors impacting on poultry gut microbiome homoeostasis, dysbiosis, and overall health. Associated infections and metabolic disorders can result from the interconnected nature of these factors. Emerging concepts (interkingdom or network signalling and neurotransmitter), and future technologies (mini-gut models, cobots) need to include these interactions to ensure accurate control and outcomes.

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Introduction

The microbiome, poultry productivity and health are all interconnected and show significant variability due to nutritional, environmental and host-related factors (Figure 1; Kers et al. 2019).

These factors affect the type and amount of pathogenic and commensal microorganisms which poultry is exposed to during growth in various farming systems. Growth stage and feeding phase and type influence the host-microbiome function and composition (Tan et al. 2019). The gut microbiome is essential to health and homoeostasis maintenance and modulation of physiological activities (immunity, metabolism, nutrition) in the host. A healthy microbiome contributes to enhancement of bird performance and productivity (Bindari and Gerber 2022; Diaz Carrasco, Casanova, and Miyakawa 2019).

There is a geometric growth in demand for poultry products (Organization for Economic Co-operation and Development/Food and Agricultural Organization 2017) and birds are effective feed converters which is key to meeting growing global demands for protein. Nonetheless, poultry are still prone to disease outbreaks especially in locations with changing micro- and macroclimates (Pin Viso et al. 2021).

The gastrointestinal tract (GIT) is densely populated with microorganisms that interact with the host and ingested feed (Pan and Yu 2014). The GIT in birds harbours a complex microbiota that conducts the key tasks of nutrient absorption and pathogen defence (O'Hara and Shanahan 2006). In pathogen defence, a protective barrier produced by the gut microbiota reduces the colonisation of pathogenic bacteria (Yegani and Korver 2008). Changes in diet and treatment interventions enhance the growth of poultry and reduce the risk of enteric infections (Kohl 2012). Interactions within the intestinal microbiome with micro-organisms, host and diet have profound effects on poultry nutrition and health (Daniel, Lecuyer, and Chassaing 2021). These interactions are a result of nutrient exchange, host gut morphology, physiology and immunity and are of great importance to poultry production (Pan and Yu 2014).

An important role for beneficial microbiota is the maintenance of normal physiological homoeostasis, host immune system modulation and metabolism (Sommer and Bäckhed 2013). Changes in the microbial community in the GIT can adversely affect poultry feed conversion efficiency, productivity and health (Kohl 2012), as well as local and systemic immune responses (Abaidullah et al. 2019).

The resident microbiota in the GIT regulates extra-intestinal immunoregulatory network of acquired immunity and promotes elimination of pathogens through opsonisation (W. H. Kim and Lillehoj 2019). The beneficial attributes of poultry commensal microbiota include competitive

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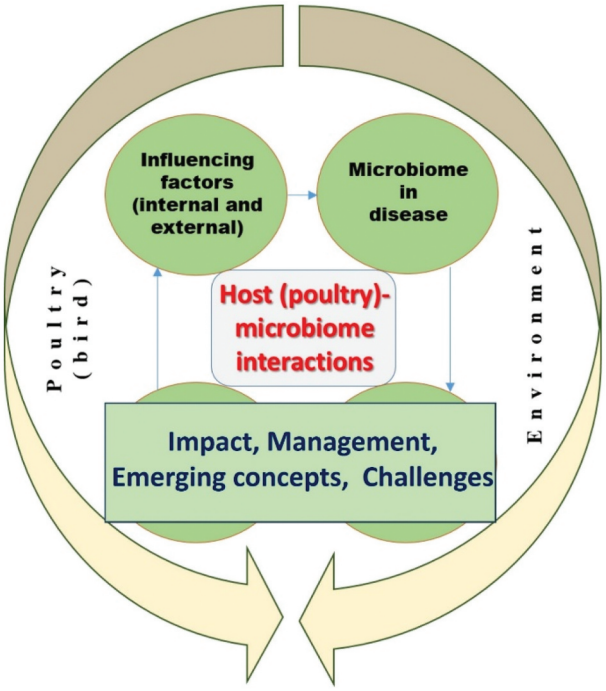

Figure 1. A conceptual overview of interacting factors, issues and concepts covered in this article.

exclusion, antibody production (immune system stimulation and development) and cytokine activation, all of which are used to protect against pathogens or non-indigenous microbes (Abaidullah et al. 2019). Stimulated immune systems include the mucus layer, epithelial monolayer and the intestinal immune cells (cytotoxic and helper T cells, immunoglobulin producing cells and phagocytic cells) (Oakley et al. 2014). These tissues play a role in developing barriers between the host and microbes to contest undesirable gut microorganisms (Mwangi et al. 2010).

The important roles for poultry GIT microbiota include nutrient absorption (Cole and Boyd 1967); enzymatic breakdown of indigestible dietary polysaccharides to their compositional fermentable sugars and short chain fatty acids (SCFA) (Dunkley et al. 2007), and welfare of the host (Hai et al. 2010). The SCFA stimulate the proliferation of epithelial cells present in the gut, increasing the absorption surface area (Dibner and Richards 2005). Additionally, the bacteriostatic properties of SCFA allows for the eradication of foodborne pathogens such as *Salmonella* spp (Ricke 2003). In addition, the microbiota stimulates metabolism of nitrogen, which is incorporated into bacterial cellular proteins allowing bacteria to serve as sources of amino acids or proteins and vitamins to the host (LeBlanc et al. 2013).

Several technologies have focussed in giving relevant insights into the interconnected nature of biotic and abiotic factors impacting poultry health and the identification and detection of associated beneficial of harmful microbiota. Some of them include bioinformatics and next-generation sequencing (NGS), 'big data' analytics, robotics and sensors, artificial intelligence (AI) and machine learning (ML) based workflows. New detection and monitoring technologies could drive the future of poultry systems management (Gowda 2023).

In light of this, this paper reviews on factors affecting the evolution of the poultry gut microbiome, associated host–microbiome interactions and the influence of microbiome disturbance (dysbiosis) in poultry disease, health and productivity. The roles of various current and emerging technologies in advancing scientific insight on the aforementioned topic under investigations are discussed.

Factors influencing the poultry gut microbiome

A healthy gut is critical to the development of intestinal immunity (Kogut 2019). The poultry microbiome is influenced by factors such as diet (Schokker et al. 2021), host (breed, sex), age or stage of life, habitat fragmentation (wild or laboratory reared) (Morrow et al. 2015) and/or environment (poultry handlers, proximity to humans, litter, access to feed, climate, location; Bindari et al. 2021). The microbiome affects animal adaptation to environmental changes, immunity development or maintenance and nutritional supplementation (Clavijo et al. 2022).

Profiling the GI microbiome is particularly important for understanding both host and gut health (Dietert and Silbergeld 2015). Fluctuations in microbiota alter the microbiome profile. Poor GI health has been linked to nutrient malabsorption and growth depression in affected poultry (Bailey 2010). The major domains related to gastrointestinal physiology, animal health and welfare include diet, digestion and absorption of dietary nutrients, resident microbiota and immune system development for disease prevention (Celi et al. 2017; Willing and Van Kessel 2010). As such, the gut plays an important role in regulating host physiological functions (Weber 2017).

Interplay of chemical and host-related factors

The interplay of physiological, nutritional, microbiological, immunological and physical characteristics of a healthy gut dictates the maintenance of intestinal homoeostasis (Polansky et al. 2016). Imbalances in the GI microbiome adversely impacts health and the GIT microbiome is key to maintaining a mutualistic relationship between the immune system of the host and the microbiome (Aruwa et al. 2021). The gut has a large surface area and is in constant interaction with the environment. Therefore, its epithelial lining has an effect in reducing exposure to toxins in the environment and provides a barrier against pathogen colonisation (Roberts et al. 2015). In a study by Lan et al. (2004), it was noted that changes in microbiome profile may result in stunted growth, weakened host resistance and susceptibility to infectious diseases. The composition of the gut microbiota is influenced by the usage of antimicrobials and exogenous feed enzymes (H. Rehman et al. 2008). The gut microbiota promotes digestion and fermentation of indigestible feed to provide essential amino acids and vitamins required by the host (Oakley and Kogut 2016). The establishment of a more favourable microbiome is necessary for optimal poultry growth and performance and, if not established, can lead to enteric infections, depressed growth rates and an increase in mortality rates (Kogut 2019).

During the passage of feed through the gut, starch hydrolysis and lactate fermentation by predominant resident *Lactobacillus* spp. (at 10^9 cells/g) occurs in the crop of poultry (Stanley, Hughes, and Moore 2014). Both mechanical and chemical degradation of the feed occurs within the gizzard (H. U. Rehman et al. 2007) and acidic conditions created in the stomach by hydrochloric acid and pepsin are key to

decreasing the microbial populations to lower than 10^8/g (Yeoman et al. 2012). Larger bacterial populations are found in the small intestine and dominated by *Lactobacillus*, *Enterococcus* and *Clostridiaceae* spp (Waite and Taylor 2015). Mash feed in broiler chickens has been shown to decrease the number of *Enterococcus* spp. and coliforms and promotes the growth of *Lactobacillus* spp. and *Clostridium perfringens* when compared to pelleted feed (Knarreborg et al. 2002). It has been reported that wheat-based diets promote bifidobacteria presence (with higher percentage of guanine-cytosine (GC) content), while corn favours a lower GC percentage of *Clostridia, Enterococci* and *Lactobacilli* spp (Apajalahti, Kettunen, and Graham 2004). Within the caeca, *Firmicutes*, *Bacteroides* and *Proteobacteria* are the dominant phyla followed by populations of *Actinobacteria*. The majority belong to various *Clostridiales* spp., known as important contributors to SCFA production (Sergeant et al. 2014). Bacteriodetes were reported to be of greater abundance, with low abundance of *Firmicutes* from d 0 to 42 as poultry birds moved from a starter to a finisher diet (Kumar et al. 2018).

The gut microbiome is an inoculum source that can be transferred from one flock to another (Liljebjelke et al. 2003). The gut is naturally colonised prior to and after hatch through transfer of microbes through eggshell pores (S. Lee et al. 2019). The transfer of innate colonisers is possible from parent fowls to offspring (Medvecky et al. 2018) and can be altered by extraneous environmental factors at various stages of development (Ding et al. 2017). Newly hatched commercial chicks generally have no contact with adult birds and the environmental microbiota promotes the development of the microbiome (Oakley et al. 2013). The post-hatch period is important for growth and health as the newly hatched chick moves from yolk to a carbohydrate and protein rich-diet (Cheled-Shoval et al. 2011). Of significance, in the developmental stages, is the microbial succession in hatchlings which start with members of the *Enterobacteriaceae* (at one-day-old poultry), followed by *Firmicutes* (at 7 d old) (Ballou et al. 2015). However, this succession with specific strains may be associated with the inherent microbiota seeded from drinking water, feed or bird interaction (Kubasova et al. 2019). The richness of the microbiome increases with time and age until it reaches maturation (Jurburg et al. 2019).

Microbiome maturation takes about 21 d in broiler chickens, but varies with farm practices and the bird's genetic background (Ngunjiri et al. 2019). Studies have shown that microbial succession in the microbiome occurs in response to the prevailing cytokine profile, such that *Proteobacteria* spp. increase in a pro-inflammatory state, while anti-inflammatory conditions favour an increase in *Firmicutes* (Oakley and Kogut 2016). Hence, the importance of the microbiome in immune balance/homoeostasis. Current studies are focused on favourably influencing the innate/early microbiome profile of poultry birds from birth *via* the infusion of probiotics, prebiotics and specific microbial consortia directly on, or into, the eggs (The Nutrition Source 2023; Rubio 2019). Interestingly, Fisinin et al. (2016) showed that the GI microbiome formation began from the embryonic stage in chicks and deemed this essential for developing healthy birds at hatching. Microbiome diversity increased with age and maturity from d 6 to 150 and only showed a decline at 300 d old. Changes in the GI microbiome composition have been observed throughout the life span (42 d) of commercial broilers. The higher abundance of beneficial bacteria and a decreased level or absence of pathogens could lead to an improvement in broiler performance (Yeoman et al. 2012) and a reduction in dietary energy requirements in chickens when unfed for long periods (Muramatsu, Nakajima, and Okumura 1994).

The use of antimicrobials in poultry farming are a necessity for disease control (Mughini-Gras et al. 2020), growth improvement and reduction in poultry morbidity and mortality (Niewold 2007). However, the removal of antibiotics in feeds can alter the homoeostasis of the gut microbiome of poultry. Poultry age and dose can further influence antibiotic effects on the gut microbiome (Zhou et al. 2007, Pedroso et al. (2013) reported that, in poultry groups grown with and without antibiotics, variations in the microbiome profile were insignificant and that it managed to stabilise and resist diversity changes after withdrawal of medication (Dethlefsen et al. 2008). Nevertheless, in recent efforts, a *Salmonella*-based phage cocktail did not show adverse impact on normal microbiome development and had the potential to serve as an alternative to antibiotics. The cocktail drastically decreased *Campylobacter* spp. populations and up-regulated levels of commensal GI microbiota that could have favourable impacts on poultry metabolism and health (Clavijo et al. 2022). In addition, the use of plant products like *Moringa oleifera* powder as alternative to antibiotics when added to feed showed favourable modulation of microbiome balance through upregulation of beneficial *Bacteroides* spp. and their metabolites (Soundararajan et al. 2023).

Given the ban on antibiotics as poultry bird growth promoters, high fibre diets are being explored as their use in moderate quantities have been linked to nutrient digestibility, enzyme secretion and organs development in poultry as a result of an enhanced gizzard function and better nutrient-enzyme contact (Mateos et al. 2012). The contribution of some amount of fibre can favourably impact poultry health. It has been suggested that fibre content of between 2% and 3% in feed, which is inclusive of insoluble fibres such as oat hulls, could enhance growth and productivity in broilers (Mateos et al. 2012). In some studies, fibre meal ratios prepared from corn, soybean and wheat bran were fed to layers and broilers to determine any effect on the caecum microbiome and SCFA levels (Sun, Hou, and Yang 2021; Walugembe et al. 2015). Fatty acid levels were shown to be higher in broilers than layers and microbiota changed under the influence of diet and chick breed. The relative prevalence of *Enterobacteriaceae* spp., *Bacteroides* spp., *Faecalibacterium* spp., *Megamonas hypermegale*, *Helicobacter pullorum* and *Campylobacter* spp. varied across chicken groups (Walugembe et al. 2015).

In addition, feed incorporated with enzymes are widely used in poultry production. These improve the performance of poultry birds by modifying the gut microbiota and gut environment (Bindari and Gerber 2022). Similarly, the use of *Saccharomyces cerevisiae* in broiler feed favourably impacts gut morphology (goblet cells, atrophy and inflammation) and reduce aflatoxin levels in chickens fed contaminated diets (Poloni et al. 2020). This can be achieved without reducing the nutritional value of the feed compared to known feed additives, for example, zeolites and clinoptilolite, which may have deleterious effects (Zain 2011), besides being used as an adsorbent for aflatoxins (Nemati et al. 2014). Likewise, *S. cerevisiae* inclusion in postbiotic feed

formulations have been shown to decrease burden of *Salmonella enterica* in chicken broilers (Chaney et al. 2022). Some members of the *Bacillus* genus, for example, *Bacillus subtilis*, have been used to enhance broilers total mean weight and GIT health under challenge conditions (Keerqin et al. 2021). Feed conversion efficiency was improved in broiler chickens with *L. pentosus* ITA23 and *L. acidophilus* ITA44 added to feed at 10^9 cells/kg of feed. *Escherichia coli* was significantly reduced, while number of *Lactobacillus* spp. increased in the caecal microbiome following supplementation (Altaher et al. 2015). *Lactobacillus* spp. (as a probiotic) in poultry feeds can contribute to effective feed conversion and absorption, as well as weight gain in poultry (Oakley et al. 2014). Villus height and perimeter within the jejunum and GI muscle thickness have been increased with the use of *Bifidobacterium thermophilum* and *Enterococcus faecium* (Chichlowski et al. 2007). Broilers serum cholesterol reduction have been achieved using an assortment of *Lactobacillus* spp (Jin et al. 1998).

In addition, prebiotic supplementation has an impact on gut microbiota composition (S. H. Lee et al. 2020). Compared to pelleted feed, coliforms and *Enterococcus* spp. populations have been reduced in poultry fed mash feed, followed by incremental increases of *C. perfringens* and *Lactobacillus* spp. in the ileum of broiler chickens (Knarreborg et al. 2002). More *Bacteroidetes* than *Firmicutes* spp. have been recorded in 0 to 42 d old birds when diets changed from starter to finisher diets. This was attributed to *Bacteroidetes* spp. ability to produce sugars from starch fermentation (Kumar et al. 2018).

Poultry health could be directly enhanced using the prebiotic fructo-oligosaccharide (FOS), which was not seen with mannan-oligosaccharide (MOS) (Xu et al. 2003). The use of FOS has been reported to improve activity of beneficial species, without impeding pathogen activity (Xu et al. 2003). The secretion of enteric mucus (mucins) is improved in the presence of MOS which contributes to the maintenance of poultry gut health. Mucus production and thickness serves as an integral line of defence against invading pathogens (Stanley, Hughes, and Moore 2014). In mildly stressed environments, MOS can increase the gut surface-area to volume ratio *via* higher goblet cell numbers in poultry (Stanley, Hughes, and Moore 2014), suppressing enteric pathogens and enhancing the immune system (Baurhoo, Phillip, and Ruiz-Feria 2007). In other studies, *Bacteroidetes* spp. populations were unaffected, while the number of *Firmicutes* spp. was higher with MOS treatment (Turnbaugh et al. 2008). Enhancement in nutrient absorption capacity of chickens has been reported for *Firmicutes* spp (Jumpertz et al. 2011). Supplementation with MOS decreased *Salmonella* spp. abundance in the caecum (Fernandez, Hinton, and Van Gils 2002) and reduced *E. coli* populations (Baurhoo, Phillip, and Ruiz-Feria 2007) in infected chickens. This was linked to mannose being able to attach to lectins in Gram-negative bacteria with type 1 fimbriae, thus decreasing the number of possible attachment sites in the epithelial cells of the gut (Ganner and Schatzmayr 2012).

Galacto-oligosaccharide (GOS) supplementation can influence the chicken gut flora by regulating the bird's innate immunity (upregulated interleukin-17A (IL-17A) expression in chicken caecum and ileum) and microbiome profile (increased relative abundance of *Lactobacillus johnsonii* in GOS-fed broilers compared to *Lactobacillus crispatus)*, giving improvements in performance (Richards et al. 2020). An increase in *Bifidobacterium* and *Lactobacillus* spp. facilitated by FOS and GOS results in an increase in SCFAs and lactate and a decrease in the colonisation of *Salmonella* spp. in both female and male broilers (Emami et al. 2012). Fructo-oligosaccharide is used as a promoter for growth and fermentation by *Bifidobacteria* spp. such as *Bifidobacterium fiagilk*, *Bifidobacterium thetaiotaomicron, Bifidobacterium vulgatus, Bifidobacterium dktasonk* and *Bifidobacterium ovatus* (Hidaka and Hirayama 1991). The secretion of the ß-fructosidase enzyme leads to FOS degradation and fermentation. In addition, the inclusion of FOS in the diets have resulted in a decline in population growth of *C. perfringens* and *E. coli* and an increase in *Lactobacillus* spp. in the broiler GIT (H. J. Kim et al. 2011). Synergistic effects can be created by supplementing with a combination of probiotics and prebiotics to create synbiotics (The Nutrition Source 2023). This has been shown to improve poultry GIT health, promote weight gain and inhibition of *Salmonella* and *Campylobacter* spp. colonisation (Ricke 2015).

Interplay of management systems and physical factors

The housing environment, climatic conditions and litter influence the presence of a more complex microbial community in the poultry gut (Shang et al. 2018). The role played by relative humidity and temperature associated with seasonal changes and external climatic conditions, especially in commercial intensive farms, are relevant factors to consider in poultry growth (Farag and Alagawany 2018). Microbiome richness and diversity in caecal samples collected during summer months has been demonstrated to be double that reported in winter (Diaz Carrasco 2019) and similar reports are available from several broiler chicken flocks in America (Oakley et al. 2018). In addition, particular management systems (Figure 1) employed within poultry farms, such as time of feeding, feed type, free range access, ventilation, heat stress, biosecurity, hygiene processes, means of treatment, vaccination program and fowl stocking density, influence the microbiome and bird productivity level (Diaz Carrasco, Casanova, and Miyakawa 2019; Göransson et al. 2023).

Bedding material can impact the prevailing microbiome (Wang et al. 2018) as birds ingest litter which accumulates in droppings, indicating a constant interaction among birds and their gut microbiome and the environment (Diaz Carrasco 2019). When litter is reused to cut poultry production costs or when high moisture litter beds are used, an increase in bacterial load is recorded which implies that disease-causing microorganisms could be transmitted among flocks (Cressman et al. 2010). Microbial colonisation of poultry from environmental sources has major biosecurity and management implications especially when there is transfer of human pathogens to consumers *via* the poultry supply chain. These risks can be mitigated by constant monitoring of the entire food supply chain (farm-to-fork) as outlined in the Food Safety Modernisation Act (Aruwa 2020; Rittenberry 2011) and should be practiced as a continuum (Oakley et al. 2013).

In other efforts, copper and zinc metals made available in a nanoscale alloy form have shown promise as mineral additives for broiler feeding and could serve as replacements for organic or inorganic sources in poultry nutrition and health.

Nanomaterials have high penetrative abilities and the metals may enter the gut and bypass transport proteins (Sizova et al. 2020). Similar results have been obtained when the arginine, methionine and lysine were delivered through iron nanoparticles in broiler chickens, leading to better weight gain (20%) and may help in increasing meat yields (Yausheva et al. 2016).

Poultry microbiome, dysbiosis, infectious and metabolic disorders

The poultry gut microbiome evolves such that, when disturbed (in a dysbiotic state), it can cause metabolic disorders. The microbiome develops immediately after hatching and diversifies to a relatively stable dynamic state (Ducatelle et al. 2023), but is readily changeable by diet, ingestion of antibiotics, infection by pathogens and other host- and environmental-dependent factors (Chow and Mazmanian 2010). Certain nutrients recognised by the innate immune system in poultry may trigger pathways that instigate disorder in nutrient metabolism and immunity, thus affecting the microbiome (Kogut 2013). The interconnected parts which make up the GI ecosystem include the commensal microbiota, immune system and intestinal epithelium. Host nutrients influence commensal diversity and host immunity impacts the microbiome (Nicholson et al. 2012). Metabolic responses and immunity are closely related, such that metabolites from the diet and microbial populations could influence inflammatory responses which give rise to metabolic disorders (Caesar, Backhed, and Bäckhed 2010). However, metabolic disease pathogenesis and aetiology in poultry may involve multifaceted conditions including gut microbiome shifts (Lavelle et al. 2010), changes in metabolism of certain nutrient-like glucose and lipids (Wen, Ting, and O'Neill 2012), rapid growth induction, excess nutrient intake which causes inflammation (Hotamisligil 2006), stress, infectious agents and toxin exposure (Julian 2005).

The GIT microbiota serves as a barrier for prevention of incoming pathogens and plays an important role in competitive exclusion for microbial attachment sites or nutrient sources (Sekirov et al. 2010). Poor gut health from an unbalanced microbiome or enteric disease results in poor poultry production (Danzeisen et al. 2013). Nutrients affect the morphology and function of the gut microbiome, as well as microbiome diversity and microbial genetics (Kogut 2022; Schokker et al. 2021). Physiological roles are provided by the gut microbiome which the host cannot provide themselves (L. C. H. Yu et al. 2012). During metabolism in microorganisms, fat storage is regulated, essential vitamins are produced and energy yield is upregulated due to the breakdown of indigestible polysaccharides in fermentation (Stecher et al. 2007). The microbiome likewise renews the gut epithelium that doubles as a barrier (Koch and Asma 2012) and contributes to xenobiotic processing, gene expression, cell differentiation and host energy. The poultry feed-microbiome interaction affects physiology, shapes immune response, balances energy, nutrient digestion and absorption, regulation and production of biologically active metabolites (Kogut 2022).

The chicken gut houses around a million bacterial genomes and over 450 phylotypes. Most caecal bacteria have only recently been identified by metagenomic methods and some remain unculturable (Sergeant et al. 2014). Microbiome plasticity is involved in some disease conditions in poultry and could facilitate dysbiosis (DB), which could give rise to infections contacted from various microorganisms (Table 1). The DB state causes a surge in circulating microbial products, such as lipopolysaccharides from the microbiome, and which innate immunity entities recognise. This state alters the ratio of beneficial to harmful strains in the gut (Kipanyula et al. 2013); hence, energy intake and generation from feed is negatively impacted (Torok et al. 2011). Complications surrounding the poultry microbiome have a significant impact on T cell receptor reserve dynamics and T lymphocytes (Ivanov et al. 2008). This suggests the presence of potent species with immunomodulatory functions. Metabolic balance/homoeostasis is directed towards host protection/immunity. The organisation of organs (adipose tissue and liver), where immune cells and macrophages are close to metabolic cells (adipocytes and hepatocytes), make maintenance of metabolic homoeostasis more evident (Hotamisligil and Erbay 2008) and these cells share signalling pathways (Henao-Mejia et al. 2012). Antibiotics are known to upset the balance of the host normal microbiota and induce a DB state. Therefore, sub-therapeutic doses of antibiotics are incorporated in a broiler diet as growth promoters and prevent diseases (Torok et al. 2011). The precise mode of action of antibiotic growth promoters (AGPs) are still not fully understood; however, withdrawal of AGPs from feed have been associated with an increased incidence of intestinal disorders (Broom 2017). Feeds supplemented with antibiotics such as avoparcin or virginiamycin have previously been used in necrotic enteritis prevention as these antibiotics alter the structure of the GIT microbiome (M. D. Lee 2008). In addition, the poultry GIT microbiome serves as a source of bacterial pathogens such as *Salmonella* and *Campylobacter* spp. that could disseminate to humans and as reservoirs of antibiotic-resistance they pose serious risks to public health *via* the food chain (Kumar et al. 2018).

In metabolically induced inflammation ('meta-inflammation' or MI), which is associated with nutrient sensing, nutrient and a surplus of metabolites serve as triggers. The MI is a chronic condition, considered a metabolic disease which leads to chronic allostasis (Hotamisligil 2006). In contrast, classical inflammation (CI) is considered acute as it triggers immune defences, is induced by invading microbes or presence of injury to the gut and is resolved by reverting to a homoeostatic state. Typical responses to CI include pain, redness, fever and swelling (Barton 2008).

In a different scenario, it has been hypothesised that the immunity-gut microbiome interaction may be linked to lameness in poultry (Kogut 2013). Due to their impact on performance and welfare, lameness and/or musculoskeletal disorders are classified as metabolic diseases (Angel 2007). Less lameness in 1 d old birds through diet supplementation with probiotics has been reported (Wideman et al. 2012). Poultry lameness is caused by bacteria, that is, chondronecrosis and osteomyelitis (Table 1) (Dinev 2009), which are translocated to the legs from the blood and GIT in a dysbiotic state and has been linked to immune suppression under stressed rearing conditions (Wideman et al. 2012).

Any alterations to the chicken microbiome can promote proliferation of pathogenic organisms (Morishita and Mitsuoka 1976). Recognised enteric disease syndromes in poultry include the runting-stunting syndrome (RSS) in young broiler chickens and PEC in young turkeys (Barnes

Table 1. Poultry microbiome groups associated with various poultry diseases.

Microbial class	Affected bird(s)	Disease/Symptom	Reference(s)
Virus			
Enteric viruses (Reoviruses, rotaviruses, astroviruses)	Turkey, chicken	Runting-Stunting Syndrome (RSS); diarrhoea	Pantin-Jackwood et al. (2008)
Chicken parvovirus (ChPV)	Chicken	RSS	Zsak et al. (2008)
Picobirnaviruses (PBVs)	Chicken	Gastroenteritis	Fregolente and Gatti (2009)
Reoviruses (fusogenic)	Most birds	Tenosynovitis	Mor et al. (2013)
Avian influenza virus (AIV)		Gastroenteritis; diarrhoea; respiratory infections	Zhang et al. (2015)
Marek's disease virus (MDV)	Chicken	Marek's disease (MD); dysbiosis; paralysis; blindness	Dunn and Gimeno (2003); Witter and Schat (2003)
Infectious bursal disease virus (IBDV)	Chicken	Infectious bursal disease (IBD); immunosuppression; secondary infections	Arega (2018); Jackwood (2017)
Avian paramyxovirus type 1 (APMV-1)	Chicken	Newcastle disease (NCD); dysbiosis	Maes et al. (2019); Abaidullah et al., (2019)
Coronavirus, calicivirus, reovirus, astrovirus, rotavirus, picornavirus, picobirnavirus, parvovirus, adenovirus	Turkey	Poult Enteritis Complex (PEC); enteritis, diarrhoea;	Barnes et al., (2000); Day et al., (2010)
Reoviruses, papovavirus, enterovirus	Turkey	Blue comb disease	Tolin and Domermuth (1975)
Picornaviruses	Turkey, duck, chicken	Enteric disease	Devaney et al. (2016); Jindal et al., (2009)
Turkey astrovirus (TAstV) and turkey coronavirus (TCoV)	Turkey	Opportunistic co-infections; poult enteritis and mortality syndrome (PEMS); immune and growth suppression	Jackwood et al. (2010); Qureshi et al., (2000)
Enteric viruses	Chicken	Pale bird syndrome	Attoui et al. (2012)
Bacteria			
Bacteria	Most birds	Bacterial chondronecrosis and osteomyelitis; Musculoskeletal disorder/lameness; inflammation	Dinev (2009); Hotamisligil (2006)
Salmonella and *Campylobacter*	Most poultry birds	Bacterial enteritis; malabsorption syndromes	European Food Safety Authority (EFSA) (2011); Songserm et al., (2000)
Clostridium perfringens	Most poultry birds	Necrotic enteritis	MacDonald et al. (2017)
Parasites, fungi and others			
Eimeria spp. (*E. acervulina*, *E. maxima*, *E. mitis*, *E. praecox*, *E. brunetti*, *E. necatrix*, *E. tenella*); and *Apicomplexa* parasites	Chicken and other poultry birds	Intestinal coccidiosis; bacterial co-infections with *Salmonella* and *C. perfringens*; nutrient malabsorption; haemorrhagic enteritis	MacDonald et al. (2017); Dhama et al., (2013) Shirley et al., (2005)
Fungi: *Microsporum gallinae*, *Dactylaria gallopava* and *Aspergillus fumigatus*	Chicken and other poultry birds	Favus, Dactylariosis, Aspergillosis. Other symptoms are allergies, inflammations, fatal infections, lesions	Dhama et al., (2013)
Fungi (feed contaminants): *Aspergillus* spp., *Fusarium* sp., *Cladosporium* sp., *Mortierella* sp., *Epicoecum* sp., *Scopulariopsis* and *Penicillium* sp.	Most poultry birds	Mycotoxicosis; other health problems	Sugiharto (2019); Vera et al., (2016)

and Guy 2003; M. J. Pantin-Jackwood 2013). Clinical symptoms of enteric disease in poultry include diarrhoea, wet litter in housing environments, reduced feed intake, dehydration, depressed growth and fluctuations in size (Barnes, Guy, and Vaillancourt 2000). *Campylobacter jejuni* is the most common cause of food-borne bacterial enteritis (European Food Safety Authority (EFSA) 2011). Still, in certain cases understanding the interplay between *C. jejuni* and poultry commensals could be key to developing new strategies to reducing its populations in broilers (Al Hakeem, Acevedo Villanueva, and Selvaraj 2023). However, this microorganism could overcome the host's defence system and compete for space and nutrients with the commensal microbial community (Awad et al. 2016). Clinically affected birds usually have pale, thin-walled intestines consisting of undigested feed. With microscopic analyses, the observation of blunted absorptive intestinal villi indicates the inability of the intestines to absorb nutrients from the feed (Songserm et al. 2000).

Diets fed to poultry before maturation and which are low in phosphorus and high in calcium can cause visceral gout leading to chronic kidney failure and bird death. Caged or sedentary hens and turkeys with unbalanced protein and energy intakes develop fatty liver syndrome (Mwato 2023). The incorporation of microencapsulated enzymes (to enhance stability and recoverability for reuse) in poultry feed could boost feed digestibility and poultry wellbeing and reduce feed cost (Maxxperformance 2023). In certain practices, chickens are hatched in the clean environment of hatcheries and the neonatal GIT may not be colonised by beneficial bacteria. This however increases the susceptibility of the chicks to pathogenic microbes that out-compete the beneficial microbes, once in direct exposure to a potent source of pathogens. Therefore, with the incorporation of probiotics or other bioactive compounds, early colonisation with healthy bacteria promotes the establishment of the intestinal microbiota and protection from pathogens (Pender et al. 2016).

The pathogenic microbiome in poultry diseases

Associated bacteriome

Some qualitative similarities in poultry microbiota have been linked to the existence of pathogens, altered GI microbiota, nutrient absorption deficiencies or poor immune development in poultry (Calvert 2012; Moussavi et al. 2007). Given the role of the GI microbiome in the production of various metabolites, studying this relative to other factors, rather than just evaluating the impact of eubiotic interventions

constitutes an explorable study niche (Kang et al. 2021). For example, in dysbacteriosis, the microbiome has been associated with visible changes in the thickness, appearance, muscle tone and tensile strength of the poultry GI wall (Collier et al. 2008). While it is common practice for poultry feed to contain high protein (Velthof, Hou, and Oenema 2015), unused nitrogen is released as ammonia (NH_3) which has a detrimental impact on health and the housing environments (Dai and Karring 2014). In broilers, NH_3 is toxic to enterocytes when absorbed through the intestinal epithelium (Rinttilä and Apajalahti 2013). Nonetheless, the incorporation of fermentable carbohydrates in the diet may reduce harmful metabolites formation from proteinaceous feeds and increase SCFAs concentrations (Heo et al. 2013).

Clostridia spp. have been implicated in dysbacteriosis, necrotic enteritis, gangrenous dermatitis and non-specific enteritis (Petersen and Round 2014) although the role played by the microbiome in diagnosis remains debateable (Daniel, Lecuyer, and Chassaing 2021). Whatever the cause of microbiome imbalances or enteric disease, the ability of poultry to efficiently utilise available nutrients in feeds is usually impacted. Indeed, financial losses are usually higher for asymptomatic and acute infections such as necrotic enteritis (Choct 2009). Bacterial pathogens that affect poultry include *Staphylococcus*, *E. coli*, *Clostridium*, *Campylobacter* and *Salmonella* spp (Oakley et al. 2014). Other poultry normal bacterial flora may become opportunistic when transferred to humans (Newell et al. 2011). In line with this, the concept of competitive exclusion has been floated as an efficient therapy to block pathogens transfer, thus enhancing GI regulation. Imitation of binding sites for pathogens in the GI epithelium using false signal binders has been shown to impede a pathogen's ability to recognise and bind to gut target sites (Oakley et al. 2014).

Associated virome

The most prevalent viruses causing runting-stunting syndrome (RSS) in chickens are the *Parvoviridae, Astroviridae, Picornaviridae, Caliciviridae, Myoviridae, Siphoviridae* and *Coronaviridae* families (Devaney et al. 2016). However, some distinct families remain unidentified and unclassified. Others include the chicken calicivirus, astrovirus, parvovirus, avian nephritis virus and novel chicken sicinivirus 1 and megrivirus. Likewise, the *Circoviridae, Adenoviridae, Picobirnaviridae, Caliciviridae, Parvoviridae, Reoviridae* and *Picornaviridae* families have been reported in healthy chicken faecal samples (Lima et al. 2017).

Asymptomatic wild birds act as pathogen reservoirs linked to emerging infectious viral disease such as West Nile virus (WNV), avian influenza virus A (H10N7) and severe acute respiratory syndrome (SARS), all of which are transmissible to humans (Mackenzie and Jeggo 2013). As reservoirs, these birds constitute a great risk to domesticated poultry. Comprehending viral diversity detection enhances the ability to predict outbreaks and transmission risks of viral diseases. Asymptomatic pathogen reservoirs contribute to virus-host coevolution and increased risk of recombinant or mutant viral strains. The asymptomatic state in poultry could be an adaptive immune response or linked to peculiar bird metabolism (Ayginin et al. 2018). A molecular technique, like DNA barcoding, has not been sufficient for the detection of many viruses since it targets majorly and only conserved regions in the genome, limiting their ability to detect new viral strains. Again, there is the lack of a general genetic marker for viral identification. Hence, universal primers for viral genome amplification and differentiation could enhance poultry virome detection, and characterisation. Interestingly, oligonucleotide designs for significant coverage and detection of known and novel viral variants in a sample, mixture of samples or biological materials have been developed (Ayginin et al. 2018), and are used to detect circovirus, avian coronavirus, Turnip yellow mosaic Virus, Tunis virus, Lake Sarah-associated circular virus-32 in Siberian Thrush (*Geokichla sibirica*) and Bean Goose (*Anser fabalis johanseni*) (Ayginin et al. 2018).

The elucidation of virome across environments, time and host species has been explored (Bergner et al. 2019) using non-invasive, untargeted shotgun metagenomic sequencing. Although difficult to characterise, the PEC and runting-stunting syndrome (RSS), among others (Table 1), in broilers are some of the syndromes associated with poultry viral infections. These infections may be mono- or polymicrobial in nature (Roussan et al. 2012). Rotaviruses cause infections alongside reovirus and astrovirus, but are detected in healthy (asymptomatic) poultry (M. Pantin-Jackwood et al. 2008). Of the five astrovirus strains, two are of turkey origin (TAstV-1 and 2), two of chicken origin (CAstV and ANV) and one originates from ducks (DAstV). While four strains are entirely host-specific, ANV was detected in both chicken and turkeys (M. Pantin-Jackwood et al. 2008). For the coronavirus family, *Coronaviridae* and genus *Gammacoronavirus* cause infectious viral enteritis in turkey (Chen, Wu, and Lin 2015). Infectious bronchitis in chickens is caused by the Infectious Bronchitis Virus (IBV), a coronavirus and can further predispose poultry to colibacillosis, followed by bacterial infections resulting in increased mortality (Matthijs et al. 2003). Stunted bird growth, reduced feed conversion efficiency, poor production, high cost of treatment, compromised immune systems and death are among the economic significances attributed to poultry diseases. The preventative control of viral disease mostly involves vaccination (Kogut et al. 2021).

Associated parasitome in poultry diseases

Parasites of the *Apicomplexa* phylum cause coccidiosis in many animals including poultry (Shirley, Smith, and Tomley 2005). This intestinal disease is caused by *Eimeria* species, but poultry response to infections caused by *Eimeria* spp. require more scientific insight (MacDonald et al. 2019). Seven species infect the *Gallus gallus domesticus* (domesticated chicken) causing malabsorptive enteritis (*Eimeria acervulina, Eimeria maxima, Eimeria mitis, Eimeria praecox*) or haemorrhagic enteritis (*Eimeria brunetti, Eimeria necatrix, Eimeria tenella*) (Shirley, Smith, and Tomley 2005). Three *Eimeria* spp., namely, *E. acervulina*, *E. maxima* and *E. tenella* are mostly found in intensively reared chickens (Clark et al. 2016). The co-infection of *Eimeria* species with bacterial pathogens such as *C. perfringens* or *S. enterica* serovars *enteritidis* or *typhimurium* could also intensify the infection. However, a healthy GIT microbiome could limit the colonisation of *Salmonella* and *Campylobacter* spp., as well as transform fungal mycotoxins present in feed to non-toxic derivatives (Hai et al. 2010). In one study, the oral administration of a chick peptide (Nk-12) expressed in *B. subtilis*

improved poultry gut and host health in broilers infected with coccidiosis (Wickramasuriya et al. 2023).

Parasite interactions with bacterial members of the poultry microbiome could be harmful or beneficial. Adverse effects include body weight loss, death, morbidity and increased costs for vaccination and control. While parasites may worsen or protect the host against inflammatory infections and DB, the microbiome could affect the parasite's virulence and ability to colonise and replicate (Leung, Graham, and Knowles 2018). The presence of *Eimeria* enhance *C. perfringens* growth in poultry gut with inhibition of beneficial bacteria (Hauck 2017). In poultry co-infection, *E. tenella* caused increase in number of *C. jejuni* gut pathogens (MacDonald et al. 2019). In another scenario, *E. tenella* coccidial disease adversely affected the caecal microbiome profile (increase in harmful *Prevotella pectinovora* and *Alistipes* sp. and reduction in probiotic microbes) and chicken health and immune responses showed expression of host transcriptomes from *Colidextribacter* sp., *Butyricicoccus porcoru* and *P. pectinovora* (H. Yu et al. 2023). Chicken lesions are also caused by the parasite *Histomonas meleagridis*, but only in the presence of bacteria (Hauck 2017). The same microbe is associated with histomonosis in turkeys (Landim de Barros et al. 2022).

Not much is known of the interaction of *Blastocystis* species with bacteria in chickens. Nevertheless, in humans, the presence of *Blastocystis* has been linked to a shift in the GIT microbiome. A similar microbiome change may be observed between the chicken gut microbiome and *Ascaridia galli*, but with the secretion of antimicrobial moieties by the parasite. While these correlations are known, the mechanisms behind these parasite-gut bacteria interactions remain a key focus of scientific inquiry (Hauck 2017). Treatment regimens for poultry parasitic infections include medications (hygromycin B, ivermectin levamisole, sulphonamide) in feed or water coupled with improved management of poultry environment (Belete, Addis, and Ayele 2016).

Associated mycobiome in poultry diseases

Most filamentous fungal species linked to poultry are contaminants of poultry feed and pathogens, but some are useful as probiotics (*S. cerevisiae*) to improve broiler fitness by producing antioxidant molecules and enzymes useful in enhancing feed quality, digestibility and poultry bird ability to resist diseases (Sugiharto 2019). The major fungal feed contaminants are the *Aspergillus* species, that is, *Aspergillus niger* and *Aspergillus flavus*. Not so dominant species include *Fusarium* sp., *Cladosporium* spp., *Mortierella* sp. and *Epicoecum* sp., which produce spores and mycotoxins (citrinin, ochratoxins, aflatoxins, oosporein, trichothecenes, ergot alkaloids) during growth (Vera, Arosemena, and Calvo-Torras 2016). The presence of allergenic fungal spores of *Scopulariopsis*, *Penicillium crysogenum*, *Aspergillus fumigatus* and *Cladosporium cladosporioides* may also initiate health challenges in poultry (Sugiharto 2019). Among the diseases caused by fungi in poultry are favus caused by *Microsporum gallinae*, dactylariosis caused by *Dactylaria gallopava* and aspergillosis linked to *A. fumigatus* (Table 1), mycotic dermatitis, among others. Such diseases lead to deadly encephalitis, mycotoxin intoxications, stunted growth and other fatal infections, amounting to economic losses. The chick's innate response tries to fight these reactions, but in the process cause further damage by activating a hypersensitivity response that brings about damage to tissues and allergies. Antifungal agents (fluco- and ketoconazole) have been used to reduce the severity of poultry fungal diseases, alongside improved sanitation, regular testing and sometimes replacement of birds with new ones (Dhama et al. 2013).

Emerging concepts and challenges in the poultry industry

The commensal poultry microbiome interacts with their host either directly (attachment to host epithelial cells) or indirectly (via interkingdom signalling). Bacterial molecules make up most of the signals recognised by the host using G-protein coupled receptors (GPRs) in the epithelium. Interkingdom signalling should constitute a key study area as protein receptors and their respective signal molecules play a key role in poultry GI health. The poultry lower gut area expresses the butyrate molecule as a signal that is central to both gut and overall poultry wellbeing (Ducatelle et al. 2023). Another key moiety in microbiome network signalling is lactate which is generated from prebiotics break down by lactobacilli or converted in broilers to butyrate by members of the family Lachnospiraceae. Unfortunately, lactate does not suffice as a metabolisable energy source for many microbes and the impact of its excess derivation and accumulation could be explored (Ducatelle et al. 2023), alongside neurotransmitter molecules producing members of the poultry microbiome and their impact on health, and additive or beneficial microbiome-induced mechanisms of action behind the use of non-starch polysaccharides (NSPs) (Ducatelle et al. 2023; E. Kim et al. 2022).

The 'omics' methods are highly automated and have greatly advanced the ability to profile microbiome features and enhance insight into pathogen and commensal functions in the gut and immune system (Kang et al. 2021). Yet, a large part of the virome network remain uncharacterised, alongside bacterium-virus co-interactions in poultry. A mechanism proposed for such co-interactions lies in the action of a mixture of phages which shape the GI function and constitution. The regulation (by viruses) of bacterial pathogenicity-related genes is another co-interaction mode of action and it is exemplified in the increased virulence in *S. enterica* in response to viral presence (Patel and Skłodowska 2023). However, significantly varied outcomes may be derived from such co-interaction studies, thus demonstrating the difficulty in comprehending co-interactions research. Still, the outcomes do not undermine the negative impact of bacterial DB and gut viral infections on poultry growth and health (Patel and Skłodowska 2023).

In spite of the foregoing, DB remains a cause and effect (Petersen and Round 2014). This scenario presents an intricate challenge because DB as an indicator of infection may also be indicative of microbiome adaptation (adaptive shift). In the latter scenario, microbiome strains which compete effectively with pathogens are increased in population and serve as an immune response (Zaneveld, McMinds, and Thurber 2017). Just as the upward regulation of beneficial to competitive microbiome does not always result in host morbidity, it may not further result in or worsen a dysbiotic state. The determinant of whether a host yields to infection or survives is virtually a consequence of the microbiome's

ability to respond to a pathogenic invasion rapidly and effectively. Beneficial microbiome shifts may achieve restoration or prevention based on the therapeutic target. It may also result from microbiome engineering (Aruwa et al. 2021; Fathima et al. 2022). Characterizing poultry GI complex microbiome and studying their impact on disease incidence and emergence, poultry performance and human health constitute an evolving research field with economic significance (Day et al. 2015). Advancements in nucleic acid sequencing techniques have expanded research possibilities regarding the exploration of microbiomes and at an unparalleled level (Yeoman et al. 2012).

Overall, poultry rearing methods could be evolved by embracing new technological frontiers in preparation for future economic shocks such as those experienced to date with the emergence of COVID-19 and to avoid significant losses in poultry meat production. Some of these include the incorporation of real time and on-site remote sensing of interconnected farming system factors. This would lead to generation of relevant big data and digitisation of the industry. The inclusion of robotics [cobots or collaborative robots that working alongside humans; and autonomous artificial intelligence (AI) based robots and sensors], use of composite housing (antimicrobial and corrosion resistant gearboxes), as well as application of nanotechnology, bioinformatics and/or big data analytics workflows (for serovars identification and detection e.g. *Salmonella*), farming system simulation prototypes, feed cast/level reporting online portals, block-chain based value management and transport genie alerting sensors (micro-climate or environment condition recorder and feedback system) could further improve poultry farming systems, production metrics, welfare and overall working conditions (Gowda 2023). Mini-gut models have also been developed and used to decrease the use of animal models in poultry research, thus facilitating the development of novel preventative and therapeutic strategies against poultry disorders (Doughman 2023). These technologies have a high propensity to shape the future of the poultry industry and contribute to enhanced production of safe and healthy poultry meats.

Conclusions

While technological advancements have improved our understanding of the poultry microbiome and their function in poultry disease and health, increasing study insight into the GIT ecosystem, range of influencing factors and host (poultry)-microbiome interactions could aid scientists in fully grasping the extent of poultry microbiome dynamics. These could also help with better understanding the emerging science of intestinal ecosystems and chat a healthier course for the treatment and management of poultry diseases. How poultry microbiome domains shift in response to environmental and growth parameters and monitoring shifts in prevalence of certain microbial species relative to particular feed formulations should remain relevant study foci. Factor to feed combinations also provide endless possibilities for exploration. Also, it is essential to combine several efficient techniques for the identification of beneficial poultry microbiome strains that play an integral role in poultry health maintenance. Nanotechnological application to diet factors could be explored to improve poultry health. Lastly, poultry GIT disease studies could be enhanced with the use of 3D mini-guts to deepen our comprehension on the poultry gut to poultry health functional interplays.

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