

## Journal of the Hellenic Veterinary Medical Society

Vol 76, No 2 (2025)



### Current challenges in porcine medicine: gut health, aspects of neonatal diarrhea, and antibiotic resistance

*N Tsekouras, LV Athanasiou, D Gougoulis, G Christodouloupoulos, C Billinis, VG Papatsiros*

doi: [10.12681/jhvms.38793](https://doi.org/10.12681/jhvms.38793)

Copyright © 2025, N Tsekouras, LV Athanasiou, D Gougoulis, G Christodouloupoulos, C Billinis, VG Papatsiros



This work is licensed under a [Creative Commons Attribution-NonCommercial 4.0](https://creativecommons.org/licenses/by-nc/4.0/).

### To cite this article:

Tsekouras, N., Athanasiou, L., Gougoulis, D., Christodouloupoulos, G., Billinis, C., & Papatsiros, V. (2025). Current challenges in porcine medicine: gut health, aspects of neonatal diarrhea, and antibiotic resistance. *Journal of the Hellenic Veterinary Medical Society*, 76(2), 8967–8978. <https://doi.org/10.12681/jhvms.38793>

## Current challenges in porcine medicine: gut health, aspects of neonatal diarrhea, and antibiotic resistance

N. Tsekouras,<sup>1\*</sup> L.V. Athanasiou,<sup>1</sup> D. Gougoulis,<sup>1</sup> G. Christodoulopoulos,<sup>2</sup> C. Billinis,<sup>3,4</sup>  
V.G. Papatsiros<sup>1</sup>

<sup>1</sup> *Clinical Veterinary Medicine Department, Faculty of Veterinary Medicine, University of Thessaly, P.O. Box 199, GR-43100, Karditsa, Greece*

<sup>2</sup> *Department of Animal Science, Agricultural University of Athens, Athens, Greece*

<sup>3</sup> *Faculty of Public and Integrated Health, University of Thessaly, 43100 Karditsa, Greece*

<sup>4</sup> *Department of Microbiology and Parasitology, Faculty of Veterinary Science, University of Thessaly, 43100 Karditsa, Greece*

**ABSTRACT:** This review explores the critical issues of gut health, neonatal diarrhea, and antibiotic resistance in swine production, underscoring the necessity for integrated management strategies. Maintaining gut health is essential for optimal pig productivity and disease resistance, with disturbances leading to substantial economic losses, particularly from neonatal diarrhea—a major cause of piglet mortality. This condition is influenced by a combination of pathogens, environmental factors, and stressors, demonstrating the need for effective prevention and control measures. Additionally, the review highlights the escalating threat of antibiotic resistance (AMR) in swine farming. Although antibiotics have been instrumental in promoting animal health, their overuse has resulted in the emergence of resistant bacteria, which pose significant challenges to both animal and human health. Notably, strains such as Extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*) exacerbate disease management complexities and can be transmitted to humans via the food chain. To combat AMR, the review advocates for stricter antibiotic usage regulations, enhanced farm management practices, and the adoption of the One Health approach, which emphasizes the interdependence of human, animal, and environmental health.

**Keyword:** Neonatal diarrhea; antibiotic resistance; swine production; One Health approach.

*Correspondence author:*

Nikolaos Tsekouras,  
Clinical Veterinary Medicine Department, Faculty of  
Veterinary Medicine, University of Thessaly, P.O. Box 199,  
GR-43100, Karditsa, Greece  
E-mail address: nitsekou@vet.uth.gr

*Date of initial submission:* 8-9-2024

*Date of acceptance:* 2-11-2024

## INTRODUCTION

The health and productivity of livestock are intricately linked to gut health, the management of neonatal diseases, and the growing challenge of antibiotic resistance. A well-functioning gut microbiome is essential for optimal digestion, nutrient absorption, and immune function, serving as the cornerstone of overall animal health (Dowarah et al., 2017). Disruptions in gut health can precipitate a cascade of health issues, most notably neonatal diarrhea—a significant concern in swine production that can lead to severe outcomes such as dehydration, stunted growth, and increased mortality (Doster, 2000).

Neonatal diarrhea, particularly in piglets, represents a persistent challenge in the swine industry, impacting productivity and animal welfare (Fairbrother et al., 2005). The vulnerability of neonatal piglets to gastrointestinal disturbances, often exacerbated by imbalances in gut microbiota, necessitates a deep understanding of the underlying causes and potential interventions (Pluske et al., 2018). Addressing these issues is crucial for improving animal health and farm productivity.

Compounding the challenges posed by gut health and neonatal diseases is the issue of antibiotic resistance, a global health crisis with profound implications for both veterinary and human medicine (WHO, 2019). The extensive use of antibiotics in livestock, particularly in swine farms, has driven the emergence of antibiotic-resistant bacteria, which pose serious threats to public health (Van Boeckel et al., 2015). The history of antibiotic use in livestock highlights the dual-edged nature of these drugs—essential for disease control yet contributing to a growing resistance problem that demands urgent attention (Economou and Gousia, 2015).

This review explores the interconnected issues of gut health, neonatal diarrhea, and antibiotic resistance in livestock, particularly swine, providing insights into their implications for animal health, public health, and sustainable livestock management practices.

### Gut Health

#### *Importance of Gut Health*

Gut health in pigs is a complex concept that extends beyond the mere absence of enteric diseases. It encompasses the overall functionality of the intestinal system, including factors such as diet, gastrointesti-

nal barrier integrity, interactions with the intestinal microbiota, efficient digestion and nutrient absorption, and immune function development (Pluske et al., 2018). Understanding gut health involves exploring how various factors, including lipid nutrition, affect gut function. For instance, dietary fatty acids can influence the gut microbiota, immune responses, and epithelial functions in piglets (Lauridsen, 2020).

Pig production plays a crucial economic role globally. In 2023, approximately 220 million pigs were produced in the European Union (EU) alone without United Kingdom (UK), making pigs the one of the largest livestock categories in the region (EC, 2024). To meet increasing demands, producers are focusing on enhancing production efficiency, meat quality, profitability, and sustainability (Maltecca et al., 2020). Despite advancements, challenges such as rising feed costs, suboptimal growth performance, and disease outbreaks persist. Research highlights the importance of the gut microbiome in maintaining pig health and nutrition. The gastrointestinal tract is essential for converting food into nutrients necessary for maintenance, growth, and immune function (Szabó et al., 2023). The gut microbiome is now considered a vital component of overall health, acting almost as an additional organ that impacts host functions and disease susceptibility (Baquero and Nombela, 2012).

The interaction between the gut microbiome and the host is crucial for health and disease development. The gut immune system plays a key role in maintaining microbial balance and intestinal homeostasis (Brody, 2020). At birth, the piglet's gut transitions from a sterile state to a microbiota-rich environment. The early-life gut microbiota, shaped by factors such as diet, antibiotics, probiotics, prebiotics, and synbiotics, plays a crucial role in health and development (Frese et al., 2015). Maintaining gut health is essential in animal production, as piglets are often exposed to stressors like birth, weaning, heat, and transport, which can impact their gut health and lead to economic losses (Cao et al., 2018).

'Gut health' is characterized by the absence of gastrointestinal complaints, the absence of bowel disease risks, and overall well-being. Bischoff (2011) proposed five criteria for gut health: efficient digestion and absorption, absence of gastrointestinal illness, a stable microbiome, effective immune status, and overall well-being. A deeper understanding of the gut microbiome's structure and function will enhance our knowledge of microbial resources and

host-microbe interactions, further advancing this field (Levin et al., 2021).

### **Effects of Antibiotics**

The swine microbiome is shaped by several factors, including age, genetics, breed, gender, and castration, with microbial diversity increasing as pigs mature (Soler et al., 2018). A diverse microbiome is crucial for health, as it helps exclude pathogens. The general composition of the pig gut microbiome at the phylum level resembled that of other mammals, with Proteobacteria, Firmicutes, and Actinobacteria making up almost 95% of the gut microbiota (Wang et al., 2029). However, early antibiotic treatments can reduce microbial diversity and cause lasting changes in the microbiome composition (Fouhse et al., 2016). Traditionally, antimicrobials have been used to eliminate pathogens, promote growth, and restore beneficial microbial communities (Holman and Chénier, 2015). Among different ages, the highest antimicrobial use in mg/kg of biomass has been recorded in suckling piglets, while the highest total use in kilograms refers to sows (Bosman et al., 2022).

Antibiotics were commonly administered in the past to treat infections and, in sub-therapeutic doses, to enhance growth and health but starting in 2019, the EU implemented measures to eliminate the routine use of antibiotics for disease prevention, limiting prophylactic use to exceptional situations in accordance with EU regulations that became effective in 2022 (Simjee and Ippolito, 2022). However, these treatments could lead to adverse effects such as antibiotic-associated diarrhea and indigestion, with *Clostridioides difficile* (*C. difficile*) infections being a notable example (Post and Songer, 2004). Broad-spectrum antibiotics disrupt both pathogenic and beneficial gut microbiota (Neuman et al., 2018).

Research has shown that antibiotics like lincosamycin can lead to reduced microbial diversity and shifts in major gut phyla, including *Firmicutes*, *Bacteroidetes*, *Spirochetes*, and *Actinobacteria* (Jo et al., 2021). Such disruptions can affect pig health, potentially leading to antibiotic-induced dysbiosis, where the gut microbiota composition is altered, impacting the gut's ability to resist pathogen colonization (Wilkins et al., 2019). Bacterial populations of *Desulfovibrio*, *Enterococcus*, *Prevotella* and members of *Erysipelotrichaceae* family found also to be affected from antimicrobial use (Tams et al., 2023). Some microbial populations may return to pre-treatment levels, while others may exhibit persistent changes (Kim et al., 2012). For example,

tylosin-treated piglets showed increased abundance of certain bacterial genera (Kim et al., 2012). In-feed antibiotics like colistin sulfate and bacitracin zinc have also caused significant shifts in gut microbiota composition (Soler et al., 2018). Gao et al. (2018b) also showed that administering ampicillin, gentamicin, and metronidazole led to a reduction in the abundance of *Lactobacillus* and *Bifidobacterium* while increasing the levels of *Shigella* species in comparison to the control pigs. Additionally, research by Li et al. (2017) indicated that early administration of amoxicillin to neonatal piglets during the first 14 days of life had temporary effects on the developing gut microbiota and resulted in a decrease in the genes associated with short-chain fatty acid signaling and pancreatic development.

Antibiotic use remains prevalent in swine production despite known risks. Therefore, understanding the impact of in-feed antibiotics on the gut microbiome is crucial for optimizing pig health and production (Jo et al., 2021).

### **Effects of Alternatives to Antibiotics**

To improve gut health and reduce reliance on antibiotics, various alternatives have been explored, including feed additives and management strategies. These alternatives aim to enhance nutrient digestion and absorption, regulate gut microbiota, and modulate immune responses. Key alternatives include amino acids, phytochemicals (essential oils), prebiotics, probiotics, and organic acids (Jiménez et al., 2020). These products aim to boost immune responses, reduce pathogen loads, promote beneficial gut microbes, and improve digestive function (de Lange et al., 2010).

Following the EU ban on antibiotics in livestock, probiotic supplementation has gained attention as a viable alternative for improving pig health and productivity (Barba-Vidal et al., 2019). Probiotics are live microorganisms that, when ingested in sufficient quantities, provide a positive effect on the health of the host (WHO, 2001). It has been also found that probiotics can modulate the gut microbiome and influence metabolite levels (Kim and Isaacson, 2015). They help regulate microbiota homeostasis and strengthen intestinal barriers, thereby improving gut health (Su et al., 2022). Studies show that supplementing piglet diets with lactic acid bacteria, such as *Lactobacillus* and *Enterococcus* species, can enhance the abundance of beneficial bacteria, reduce harmful bacteria like *E. coli*, and increase short-chain fatty acid production (Su et al., 2022).

Specific probiotics, like *Lactobacillus salivarius* and *Enterococcus faecium*, have been shown to improve gut microbiota diversity in piglets (Pajarillo et al., 2015). Further research is needed to fully understand the roles of probiotics in modulating piglet microbiota and immune responses.

Essential amino acids are vital for pig nutrition, as pigs cannot synthesize them in adequate amounts. Supplementing diets with essential amino acids is crucial for maintaining nitrogen balance, supporting growth, and enhancing immunity (Chen et al., 2009). Amino acids such as threonine, lysine, methionine, tryptophan, and glutamine have shown benefits in promoting beneficial microbiota growth, reducing intestinal ammonia levels, and suppressing opportunistic pathogens (Liao et al., 2024). Further research is needed to explore the interactions between dietary fiber and amino acids and their combined effects on gut microbiota. With the global shift away from in-feed antibiotics and medicinal zinc oxide, investigating the specific effects of amino acids on gut microbiota composition and function is essential (Liao, 2021). Additional studies should focus on microbial metabolism of amino acids and their implications for pig intestinal health (Ma et al., 2021).

Prebiotics, defined as “non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of specific bacteria in the colon,” are gaining attention as potential alternatives to antibiotics and antimicrobials (Gibson et al., 2017). Novel prebiotics, although not yet fully understood, may offer health benefits by selectively supporting beneficial gut microbes. Identifying the most effective prebiotics for different developmental stages and understanding their mechanisms are critical for maximizing their benefits (Kiernan et al., 2023). Regarding piglets, past study has shown that the oral administration of prebiotics, as fructooligosaccharides, to newborn piglets leads to an increase in the body weight of the litter at weaning and improved intake of pre-starter feed (Zivkovic et al., 2011). In older age groups, such as weaned pigs, chitooligosaccharides and fructooligosaccharides have been found to positively influence average daily gain and reduce both the incidence and severity of diarrhea (Liu et al., 2008; Liu et al., 2020).

Organic acids are defined as any organic carboxylic acids, which may include keto or hydroxyl groups but exclude amino acids, characterized by the general R-COOH structure (Khan and Iqbal,

2016). These acids are prevalent in nature as normal components of plant and animal tissues and are produced either through chemical synthesis or microbial fermentation of carbohydrates in the large intestine (Hajati, 2018). The exact mechanisms of action for common acidifiers are not yet fully understood. However, their effectiveness may be partially attributed to several factors: a) inhibiting the growth of pathogenic microbes in the GIT by lowering gut pH (e.g. lactic acid), b) reducing gastric emptying rates and supporting the secretion of endogenous enzymes (e.g. citric acid), c) chelating minerals and stimulating intermediary metabolism (e.g. fumaric acid), and d) aiding proper digestion through lower gastric pH and increased (e.g. acetic acid) pepsin secretion (Papatsiros and Billinis, 2012; Rathnayake et al., 2021).

## Aspects of Neonatal Piglet Diarrhea

### *Understanding Neonatal Piglet Diarrhea*

Neonatal piglet diarrhea presents a significant challenge in modern swine farming, leading to high mortality rates, decreased growth, and increased treatment costs (Sjölund et al., 2014). The neonatal period, which spans the first few days to a week after birth, is particularly vulnerable to such outbreaks (Mesonero-Escuredo et al., 2018). Various factors—both infectious and non-infectious—contribute to disease susceptibility in suckling piglets. Stress, suboptimal management, and inadequate nutrition are notable contributors (Vidal et al., 2019). Common pathogens include *E. coli*, clostridia [*Clostridium perfringens* (*C. perfringens*) type C and type A, *Clostridioides difficile* (*C. difficile*)], *Enterococcus hirae* (*E. hirae*), coronaviruses, rotaviruses and *Cystoisospora suis* (*C. suis*) (Jacobson, 2022). Although these pathogens can individually cause diarrhea, co-infections are often observed (Kongsted et al., 2018). Clinical signs vary based on the pathogen, infection load, and piglet immunity, complicating the attribution of specific symptoms to particular causes (Morin et al., 1983). The diverse pathogen combinations and disease scenarios across farms highlight the multifactorial nature of neonatal diarrhea, emphasizing the need for tailored diagnosis and management strategies at the farm level. Non-infectious factors also need to be considered in disease management (Vidal et al., 2019).

### *Escherichia coli*

The gastrointestinal tract of newborn piglets quickly becomes colonized by bacteria, including *E. coli*, through exposure to other piglets, their surroundings,

and sow feces (Dubreuil, 2021). Swine colibacillosis, caused by *E. coli*, leads to issues such as neonatal diarrhea, post-weaning diarrhea (PWD), edema disease (ED), septicemia, polyserositis, coliform mastitis, and urinary tract infections (Fairbrother and Nadeau, 2019). This infection has significant financial implications due to reduced body weights, slowed growth, and increased treatment costs (Barros et al., 2023). *E. coli* pathogens include enteropathogenic *E. coli* (EPEC), enterohaemorrhagic *E. coli* (EHEC), enteroaggregative *E. coli* (EAEC), enteroinvasive *E. coli* (EIEC), diffusely adherent *E. coli* (DAEC), and enterotoxigenic *E. coli* (ETEC) (Kaper et al., 2004). ETEC, in particular, is a primary cause of diarrhea in neonatal piglets, with fimbriae such as F4, F5, F6, and F41 associated with the condition (Luppi et al., 2016). ETEC binds to receptor sites on epithelial cells in the jejunum, leading to enterotoxin production and excessive fluid and electrolyte secretion. Symptoms include watery to creamy scours, with potential dehydration and metabolic acidosis (Fairbrother and Nadeau, 2019). EPEC also causes diarrhea but affects the entire intestine (DebRoy and Maddox, 2001). Diagnosis involves clinical observation, bacteriological investigations, and strain typing. Treatment is costly and involves antibiotics such as amoxicillin/clavulanic acid, ceftiofur, and others (Luppi, 2017). Resistance to antibiotics is a concern, highlighting the need for prudent use and susceptibility testing (Barros et al., 2023). Despite advances in research and vaccine development, ETEC remains a significant issue (Wang et al., 2019), with maternal exposure and antibody levels influencing vaccine efficacy (Nadeau et al., 2017).

### **Clostridia**

Clostridia are gram-positive, spore-forming bacilli that can cause enteric diseases in various animals, including swine (Rood, 2016). *C. perfringens* type C and *Clostridioides difficile* are significant pathogens in neonatal swine (Diab et al., 2016). *C. perfringens* type A's role in piglet diarrhea is debated, but it is implicated in some cases (Uzal et al., 2016). Recent studies have linked clostridia to various pathogens in neonatal diarrhea, complicating diagnosis and management (Vidal et al., 2019). *C. perfringens* is found in soil, decaying matter, and animal feces (McClane et al., 2013), and causes rapid-onset disease in young piglets with distinct clinical signs and necropsy findings. Effective prevention involves vaccinating pregnant sows and improving environmental conditions (Silva et al., 2015). *C. perfringens* type C strains carry toxin genes and cause varying clinical

presentations (Rood et al., 2018). *C. difficile*, first reported in swine in 1983 (Jones and Hunter, 1983), can cause disease in piglets with disrupted gut flora. Clinical signs include diarrhea, respiratory distress, and high mortality rates, with pathology showing inflammation and edema (Songer et al., 2000). Improved hygiene and stress reduction are effective prevention strategies (Nagy and Bilkei, 2003). Diagnosing clostridial diseases requires consideration of various factors, including management practices and environmental conditions (Uzal et al., 2023). Vaccination of sows with inactivated culture supernatants helps reduce mortality in litters (Posthaus et al., 2020).

### **Enterococcus spp.**

The *Enterococcus* species are a commensal bacterium in the GIT of animals, while members of the genus group III are involved in neonatal piglet diarrhoea (Facklam et al., 2002). The pathogenesis remains unclear, but it may be linked to reduced activity of brush border enzymes and disruptions in digestion and absorption processes. Three main species are reported to be associated with neonatal piglet diarrhoea: *E. villorum*, *E. durans*, and *E. hirae* (Vancanneyt et al., 2001). Lesions related to *E. durans* are caused by the extensive colonization of the small intestinal enterocytes by Gram-positive cocci and a few sloughed enterocytes (Cheon and Chae, 1996). Lesions related to *E. hirae* are characterized by consisted of flaccid and dilated intestines with liquid to creamy content, while numerous Gram-positive cocci were associated with villous epithelial damage and atrophy (Jang et al., 2019). In cases of neonatal piglet diarrhoea, the amount of *Enterococcus* spp. was up to 24 times more abundant in the intestinal content of sick piglets in comparison to healthy piglets, revealing the important role of *Enterococcus* spp. has in the pathogenesis of neonatal piglet diarrhoea (Gryaznova et al., 2022).

### **Coronaviruses**

Coronaviruses are a major cause of neonatal piglet diarrhea globally (Liu et al., 2021). Six coronaviruses affect pigs, including TGEV, PRCV, PEDV, SADS-CoV, PHEV, and PDCoV (Wang et al., 2019). TGEV causes transmissible gastroenteritis (TGE), leading to severe gastrointestinal symptoms and high mortality in piglets (Doyle and Hutchings, 1946). TGEV spreads through fecal-oral, respiratory, and breastfeeding routes, with symptoms appearing two weeks post-exposure (Enjuanes et al., 1995). The incidence of TGEV has decreased due to vaccination

(Zhang et al., 2019). PEDV, first identified in the UK in 1971, causes severe enteric disease with high mortality rates in piglets (Song and Park, 2012). Recent highly pathogenic variants have caused significant economic losses globally (Li et al., 2020). PEDV infections lead to high mortality and long-term performance issues in surviving piglets (Alvarez et al., 2015). Biosecurity and vaccination are key to controlling TGEV and PEDV. Both live attenuated and inactivated virus vaccines are used, focusing on the spike protein (Liu and Gerdt, 2021).

### **Rotavirus**

Rotavirus (RV) is classified as A–J based on antigenic properties, while RV groups A, B, and C are most identified (Vlasova et al., 2017). RVA to RVE and RVH have been reported in pigs, and RVA to RVC may be involved in neonatal piglet diarrhoea (Marthaler et al., 2013). The clinical symptoms observed in experimentally infected piglets (aged 2 to 28 days) encompass lethargy, loss of appetite, vomiting, severe diarrhea, and a swift decline in overall health (Theil et al., 1985). In naïve herds, the clinical signs in 1–2 days-old piglets are characterized by within-litter morbidity of 100%, and mortality rates of 5–10% (Morin et al., 1990). Subclinical infections are common, while the age of onset is related to the level of maternal immunity, which may suppress the development of active immunity (Vlasova et al., 2017).

### **Cystoisospora suis**

*Cystoisospora suis* (formerly *Isospora suis*) is a prevalent pathogen in suckling piglets, with significant economic impact due to weight reduction at weaning (Maes et al., 2007). *C. suis* infection occurs shortly after birth, with oocysts ingested from the environment. Infected piglets exhibit inflammation and lesions in the small intestine (Taylor et al., 2016). Diagnosis requires sensitive detection methods and repeated fecal sampling (Joachim et al., 2018). Prevention involves stringent hygiene measures and disinfection, although oocysts are resistant to common disinfectants (Hinney et al., 2020). Toltrazuril is an effective drug, but resistance to anticoccidials is a growing concern (Gong et al., 2021).

## **Antibiotic Resistance**

### **Overview of Antibiotic Resistance in Swine**

Antibiotic resistance (AMR) represents a growing global health challenge, affecting both human and veterinary medicine. In swine farming, although an-

tibiotics play a key role as a therapeutic approach, their use significantly contributes to the development of antimicrobial resistance (AMR). This section examines the prevalence, causes, and consequences of AMR in swine farms.

AMR is notably prevalent in swine, particularly due to intensive farming practices that involve frequent antibiotic use. For example, regarding the zoonotic bacteria *Salmonella* spp., in 2021, resistance rates were recorded in samples from fattening pigs under one year of age at 10.1%, while the multidrug resistance of *Salmonella* was 39.1% (EFSA, 2024). Research highlights high levels of resistant bacteria in pigs, including strains producing extended-spectrum beta-lactamases (ESBLs), which resist a wide range of beta-lactam antibiotics. For instance, recent studies in Greece found that 36.5% of bacterial isolates from pigs were resistant to third-generation cephalosporins, illustrating the extent of the issue (Tsekouras et al., 2022).

Key factors contributing to AMR include the overuse and misuse of antibiotics (Byrne et al., 2019). These drugs are often administered not only for treatment but also for prophylaxis and growth promotion. Such practices create selective pressure favoring resistant strains. Inadequate dosing and incomplete treatment further exacerbate the problem, allowing resistant bacteria to thrive.

Horizontal gene transfer among bacteria, facilitated by the dense populations in intensive farming, also plays a crucial role. Poor farm management practices, including inadequate biosecurity and hygiene, contribute to the spread of resistant bacteria (Poudel et al., 2024).

The implications of AMR are severe. For the livestock sector, AMR increases morbidity and mortality rates, reduces productivity, and imposes economic losses (Innes et al., 2020). The reduced effectiveness of common antibiotics necessitates the use of more potent and costly alternatives.

From a public health perspective, AMR poses a significant threat. Resistant bacteria can transfer to humans through direct contact with animals, consumption of contaminated meat, and environmental exposure (Xu et al., 2022). This zoonotic transfer can lead to difficult-to-treat infections, prolonged illnesses, and higher healthcare costs (Almansour et al., 2023). Additionally, the rise of multi-drug-resistant bacteria undermines the efficacy of critical antibiotics in both human and veterinary medicine.

Combating AMR requires a comprehensive approach. Stricter regulations on antibiotic use, enhanced surveillance, and improved farm management practices are essential (Muteeb et al., 2023). Promoting alternatives like probiotics and prebiotics can help reduce antibiotic dependency. The One Health approach, integrating human, animal, and environmental health, is crucial for developing effective strategies against AMR.

In summary, addressing AMR in swine farming is urgent and requires coordinated efforts. Understanding AMR's prevalence, causes, and impacts, and implementing effective strategies can protect animal health, public health, and the sustainability of the livestock industry.

### ***History of Antibiotic Use in Livestock***

Since the mid-20th century, antimicrobial agents have been widely utilized in livestock to enhance productivity and safeguard animal health (Lekagul et al., 2019). Initially, these agents were employed primarily for treatment, but their use expanded to include prophylaxis and growth promotion (Kimera et al., 2020).

The benefits of antimicrobials in growth promotion were recognized as early as the late 1940s, with Stockstad and Jukes demonstrating their efficacy in poultry and pig production (Stockstad and Jukes, 1949). By the 1960s, extensive research had been published on antimicrobials as growth promoters (Thoms, 2012). However, Alexander Fleming's early observations of resistance highlighted the need for cautious use (Fleming, 1945).

Concerns about the negative impacts of excessive antimicrobial use emerged around 1965, but the demand for animal protein and cost reductions often outweighed these concerns (Kirchhelle, 2018). Antimicrobials were routinely used therapeutically, metaphylactically, and prophylactically (Callens et al., 2012).

The rise in living standards and animal protein consumption led to intensified livestock production and increased antimicrobial use (Dall, 2018). Despite the economic advantages, excessive antimicrobial use was criticized for promoting resistance (Kirchhelle, 2018). The European ban on antibiotic growth promoters, effective from 2006, reflected growing awareness of these issues (EC, 2003). In 2022, a total of 4,458 tonnes of antimicrobials were used in farm animals across the EU, with the main classes being penicillins (32.7%), tetracyclines (23.5%), and

sulfonamides (9.4%), which together accounted for 65.5% of total sales (EMA, 2023).

### ***The Rise of Antibiotic Resistance***

The livestock sector is a major contributor to global antimicrobial resistance (DANMAP, 2018). Antimicrobials, originally intended for therapeutic use, have often been used to boost productivity and cover up poor management practices (Dewulf et al., 2022). In 2013, over 130,000 tons of antimicrobials were used in animal production, and usage is projected to exceed 200,000 tons by 2030 (Van Boeckel et al., 2017). Despite regulatory efforts, resistance remains a pressing issue, with resistance genes found in a significant proportion of livestock (Argudin et al., 2017). In recent past several studies revealed a positive correlation between antimicrobial consumption in farm animals and increased AMR in humans (Aarstrup, 2012; George, 2018; Arkadani et al., 2023).

Pig production, crucial for meeting global protein demands, has been linked to significant resistance issues. The use of critically important antimicrobials like colistin in pigs for treating *E. coli* infections raises concerns (Rhouma et al., 2016). The discovery of the colistin-resistant gene MCR-1 and increasing resistance in *E. coli* strains highlight the severity of the problem (Liu et al., 2016).

The spread of resistant bacteria is facilitated by factors such as manure use and environmental contamination (Kim et al., 2010). Climate change and decreased biodiversity also contribute to resistance (Hoberg and Brooks, 2015). Despite limited data from developing countries, the global impact of AMR is evident, stressing the need for international collaboration (Van Boeckel et al., 2019).

### ***Public Health Implications***

Antimicrobial-resistant bacteria from livestock pose significant public health risks through direct contact with animals, consumption of contaminated meat, and environmental exposure (Founou et al., 2016). The excessive use of antimicrobials in both humans and animals is a leading cause of resistance, threatening food security and human health (Founou et al., 2021). The World Health Organization projects that antimicrobial resistance could lead to 10 million deaths annually by 2050 (WHO, 2019).

Antimicrobial resistance impacts various aspects of health and economics. Bacteria resistant to common treatments necessitate the use of last-line drugs, which are costly and less accessible in low-income

countries (WHO, 2015). Recent studies link antimicrobial resistance to significant economic losses, including increased medical costs and decreased productivity (Innes et al., 2020). The need for new antimicrobials and changes in global trade practices further compound these issues (Lekagul et al., 2019).

### ***Economic Consequences***

The economic burden of antimicrobial resistance (AMR) is substantial. In the USA, AMR-related costs are estimated at \$3 billion annually, with significant future economic losses predicted (Ahmad and Khan, 2019). AMR leads to higher healthcare costs and loss of productivity, with the potential to impact global economies severely (Innes et al., 2020). The inefficacy of current antimicrobials forces reliance on expensive alternatives, further straining resources and affecting trade (WHO, 2015).

Efforts to mitigate AMR must focus on reducing antimicrobial use, improving farm management practices, and fostering international collaboration to balance animal welfare, consumer expectations, and sustainable development (Monger et al., 2021).

### **CONCLUSION**

The interconnected challenges of gut health, neonatal diarrhea, and antibiotic resistance in swine production present significant concerns that demand a comprehensive and integrated approach. Gut health

plays a critical role in ensuring optimal growth and disease resistance in pigs, with disruptions leading to severe conditions like neonatal diarrhea—a major cause of mortality and economic loss in the industry. Addressing these issues requires not only targeted prevention strategies against pathogens and environmental stressors but also a broader understanding of the underlying factors that contribute to gut dysbiosis.

Moreover, the review underscores the escalating threat of antibiotic resistance, exacerbated by the overuse of antibiotics in swine farming. The emergence of resistant bacteria such as ESBL-producing *Escherichia coli* poses severe risks, extending beyond animal health to threaten public health through the food chain. To mitigate these risks, it is imperative to implement stricter antibiotic regulations, improve farm management practices, and adopt the One Health approach, which emphasizes the interconnectedness of human, animal, and environmental health. By embracing these strategies, the swine industry can safeguard both animal and public health while promoting sustainable and responsible farming practices.

### **CONFLICT OF INTEREST**

The authors declare that there is no conflict of interest.

## **REFERENCES**

- Aarestrup F (2012) Get pigs off antibiotics. *Nature* 486:465-466.
- Ahmad M, Khan AU (2019) Global economic impact of antibiotic resistance: A review. *J Glob Antimicrob Resist* 19:313-316.
- Almansour AM, Alhadlaq MA, Alzahrani KO, Mukhtar LE, Alharbi AL, Alajel SM (2023) The Silent Threat: Antimicrobial-Resistant Pathogens in Food-Producing Animals and Their Impact on Public Health. *Microorganisms* 11(9):2127.
- Alvarez J, Sarradell J, Morrison R, Perez A (2015) Impact of Porcine Epidemic Diarrhea on Performance of Growing Pigs. *PLOS ONE* 10(3):e0120532.
- Argudin MA, Deplano A, Meghraoui A, Dodemont M, Heinrichs A, Denis O, Nonhoff C, Roisin S (2017) Bacteria from animals as a pool of antimicrobial resistance genes. *Antibiotics* 6:12.
- Ardakani Z, Canali M, Aragrande M, Tomassone L, Simoes M, Balzani A, Beber CL (2023). Evaluating the contribution of antimicrobial use in farmed animals to global antimicrobial resistance in humans. *One Health* 17:100647. doi: 10.1016/j.onehlt.2023.100647.
- Baquero F, Nombela C (2012) The microbiome as a human organ. *Clin Microbiol Infect* 18:2-4.
- Barba-Vidal E, Martín-Ortíz SM, Castillejos L (2019) Practical aspects of the use of probiotics in pig production: a review. *Livest Sci* 223:84-96.
- Barros MM, Castro J, Araújo D, Campos AM, Oliveira R, Silva S, Outor-Monteiro D, Almeida C (2023) Swine Colibacillosis: Global Epidemiologic and Antimicrobial Scenario. *Antibiotics* 12(4):682.
- Bischoff SC (2011) 'Gut health': a new objective in medicine? *BMC Med* 9:24.
- Bosman AL, Deckert AE, Carson CA, Poljak Z, Reid-Smith RJ, McEwen SA (2022) Antimicrobial use in lactating sows, piglets, nursery, and grower-finisher pigs on swine farms in Ontario, Canada during 2017 and 2018. *Porc Health Manag* 8(1):17. doi: 10.1186/s40813-022-00259-w.
- Brody H (2020) The gut microbiome. *Nature* 577:S5.
- Byrne MK, Mielle S, McGlenn A, Fish J, Meeya S, Reynolds N, van Oijen AM (2019) The drivers of antibiotic use and misuse: the development and investigation of a theory driven community measure. *BMC Public Health* 19(1):1425.
- Callens B, Persoons D, Maes D, Laanen M, Postma M, Boyen F, Haesebrouck F, Butaye P, Catry B, Dewulf J (2012) Prophylactic and metaphylactic antimicrobial use in Belgian fattening pig herds. *Prev Vet Med* 106:53-62.
- Cao ST, Wang CC, Wu H, Zhang QH, Jiao LF, Hu CH (2018) Weaning disrupts intestinal antioxidant status, impairs intestinal barrier

- and mitochondrial function, and triggers mitophagy in piglets. *J Anim Sci* 96(3):1073–83.
- Chen L, Li P, Wang J, Li X, Gao H, Yin Y, Hou Y, Wu G (2009) Catabolism of nutritionally essential amino acids in developing porcine enterocytes. *Amino Acids*. 37:143–152.
- Cheon DS, Chae C (1996) Outbreak of diarrhea associated with *Enterococcus durans* in piglets. *J Vet Diagn Investig* 8:123–124.
- Dall C. Global antibiotic use rises, fueled by economic growth (2018). Available at: <http://www.cidrap.umn.edu/news-perspective/2018/03/global-antibiotic-use-rises-fueled-economic-growth>. Accessed on 25 September 2021.
- DANMAP (2018) Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food, and humans in Denmark. Danish Integrated Antimicrobial Resistance Monitoring and Research Programme.
- De Lange C, Pluske J, Gong J, Nyachoti GM (2010) Strategic use of feed ingredients and feed additives to stimulate gut health and development in young pigs. *Livest Sci* 134(1-3).
- DeRoy C, Maddox CW (2001) Identification of virulence attributes of gastrointestinal *Escherichia coli* isolates of veterinary significance. *CAB Int* 1:129–140.
- Dewulf J, Joosten P, Chantziaras I, Bernaerdts E, Vanderhaeghen W, Postma M, Maes D (2022) Antibiotic Use in European Pig Production: Less Is More. *Antibiotics* 11:1493.
- Diab SS, Uzal FA, Songer JG (2016) Diseases Produced by *Clostridium difficile*. In: Uzal FA, Songer JG, Prescott JF, Popoff MR (Eds.), *Clostridial Diseases of Animals*. John Wiley & Sons, Inc, Hoboken, NJ, pp. 177–195.
- Doster A (2000) Porcine gastric ulcer. *Vet Clin N Am Food Anim Pract* 16:163–174.
- Dowarah R, Verma AK, Agarwal N, Patel BHM, Singh P (2017) Effect of swine based probiotic on performance, diarrhoea scores, intestinal microbiota and gut health of grower-finisher crossbred pigs. *Livest Sci* 195:74–79
- Doyle LP, Hutchings LM (1946) A transmissible gastroenteritis in pigs. *J Am Vet Med Assoc* 108:257–259.
- Dubreuil JD (2021) Pig vaccination strategies based on enterotoxigenic *Escherichia coli* toxins. *Braz J Microbiol* 52(4):2499–2509.
- Economou V, Gousia P (2015) Agriculture and food animals as a source of antimicrobial-resistant bacteria. *Infect Drug Resist* 8:49–61.
- European Food Safety Authority (2024) The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2021–2022. *EFSA J* 21(2):e8583.
- European Medicines Agency. (2023). Sales of veterinary antimicrobial agents in 31 European countries: 2022 trends (2010–2022). Available at: [https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2022-trends-2010-2022-thirteenth-esvac-report\\_en.pdf](https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2022-trends-2010-2022-thirteenth-esvac-report_en.pdf). Accessed on 25 September 2024.
- Enjuanes L, Smerdou C, Castilla J, Antón IM, Torres JM, Sola I, Golvano J, Sánchez JM, Pintado B (1995) Development of protection against coronavirus induced diseases. A review. *Adv Exp Med Biol* 380:197–211.
- European Commission (2024). Pigmeat Dashboard. Available at [https://agridata.ec.europa.eu/Reports/Pigmeat\\_Dashboard.pdf](https://agridata.ec.europa.eu/Reports/Pigmeat_Dashboard.pdf). Accessed on 25 September 2024.
- European Parliament and the Council of the European Union Regulation (EC) No 1831/2003. *Off. J. Eur. Union* 2003, 4:29–43. Available at: <http://eur-lex.europa.eu/legal-content/PT/TXT/?uri=celex:32003R1831> Accessed on 17 February 2021.
- Facklam RR, Carvalho MG, Teixeira LM (2002) *Enterococcus*. In: Gilmore MS, Clewell DB, Courvalin P, Dunne GM, Murray BE, Rice LB, (eds) *The Enterococci: Pathogenesis, Molecular Biology, and Antibiotic Resistance*. ASM Press, Washington, DC, USA, pp. 1–54.
- Fairbrother JM, Nadeau É. Colibacillosis. In: Zimmerman JJ, Karriker LA, Ramirez A, Schwartz KJ, Stevenson GW, Zhang J (eds). *Diseases of Swine*. John Wiley & Sons; Hoboken, NJ, USA: 2019. pp. 807–834.
- Fairbrother JM, Nadeau E, Gyles CL (2005) *Escherichia coli* in post-weaning diarrhea in pigs: an update on bacterial types, pathogenesis, and prevention strategies. *Anim Health Res Rev*. 6(1):17–39.
- Fleming A. Penicillin; Nobel Lecture; 11 December 1945; pp. 84–93. Available at: <https://www.nobelprize.org/prizes/medicine/1945/fleming/lecture/>. Accessed on 24 July 2020.
- Fouhse JM, Zijlstra RT, Willing BP (2016) The role of gut microbiota in the health and disease of pigs. *Anim Front* 6(3):30–6. <https://doi.org/10.2527/af.2016-0031>
- Founou LL, Founou RC, Essack SY (2016) Antibiotic resistance in the food chain: A developing country-perspective. *Front Microbiol* 7:1881.
- Founou LL, Founou RC., Essack S. Y. (2021) Antimicrobial resistance in the farm-to-plate continuum: more than a food safety issue. *Futur Sci FSO692*.
- Frese SA, Parker K, Calvert CC, Mills DA (2015) Diet shapes the gut microbiome of pigs during nursing and weaning. *Microbiome* 3:28.
- Gao K, Pi Y, Peng Y, Mu CL, Zhu WY (2018b) Time-course responses of ileal and fecal microbiota and metabolite profiles to antibiotics in cannulated pigs. *Appl. Microbiol. Biotechnol* 102:2289–2299.
- George A (2018) Antimicrobial resistance, trade, food safety and security. *One Health* 5:6–8.
- Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, Scott K, Stanton C, Swanson KS, Cani PD, Verbeke K, Gregor R (2017) Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol* 14:491–502.
- Gong Q-L, Zhao W-X, Wang Y-C, Zong Y, Wang Q, Yang Y, Yang Y, Shi K, Li J-M, Leng X, Du R, Zhao Q (2021) Prevalence of coccidia in domestic pigs in China between 1980 and 2019: a systematic review and meta-analysis. *Parasit Vectors* 14:248.
- Gryaznova MV, Dvoretzkaya YD, Syromyatnikov MY, Shabunin SV, Parshin PA, Mikhaylov EV, Strelnikov NA, Popov VN (2022) Changes in the microbiome profile in different parts of the intestine in piglets with diarrhea. *Animals* 12:320.
- Hajati H (2018) Application of organic acids in poultry nutrition. *Int J Avian Wildl Biol* 3:324–329.
- Hinney B, Cvjetkovic V, Espigares D, Vanhara J, Waehner C, Ruttkowski B, Selista R, Sperling D, Joachim A (2020) *Cystoisospora suis* control in Europe is not always effective. *Front Vet Sci* 7:113.
- Hoberg EP, Brooks DR (2015) Evolution in action: Climate change, biodiversity dynamics and emerging infectious disease. *Philosoph Trans R Soc B* 370, 20130553.
- Holman DB, Chénier MR (2015) Antimicrobial use in swine production and its effect on the swine gut microbiota and antimicrobial resistance. *Can J Microbiol* 61:785–798.
- Innes G, Randad PR, Korinek A, Davis MF, Price LB, So AD, Heaney CD (2020) External Societal Costs of Antimicrobial Resistance in Humans Attributable to Antimicrobial Use in Livestock *Annu Rev Public Health* 41:141–157.
- Jacobson M (2022) On the Infectious Causes of Neonatal Piglet Diarrhoea—A Review. *Vet Sci* 9:422.
- Jang S, Shin S, Kim S-H, Kim H, Moon C (2019) Diagnosis of *Enterococcus hirae* infection in association with piglet diarrhea. *J Biomed Transl Res* 20:115–120.
- Jiménez MJ, Berrios R, Stelzhammer S, Bracarense APFRL (2020) Ingestion of organic acids and cinnamaldehyde improves tissue

- homeostasis of piglets exposed to enterotoxigenic *Escherichia coli* (ETEC). *J Anim Sci* 98:skaa012.
- Jo HE, Kwon MS, Whon TW, Kim DW, Yun M, Lee J, Shin MY, Kim SH, Choi HJ (2021) Alteration of Gut Microbiota After Antibiotic Exposure in Finishing Swine. *Front Microbiol* 12:596002.
- Joachim A, Ruttkowski B, Sperling D (2018) Detection of *Cystoisospora suis* in faeces of suckling piglets - when and how? A comparison of methods. *Porcine Health Manag* 4:20.
- Jones MA, Hunter D (1983) Isolation of *Clostridium difficile* from pigs. *Vet Rec* 112:253–254.
- Kaper JB, Nataro JP, Mobley HL (2004) Pathogenic *Escherichia coli*. *Nat Rev Microbiol* 2(2):123–140.
- Khan SH, Iqbal J (2016) Recent advances in the role of organic acids in poultry nutrition. *J Appl Anim Res* 44:359–369.
- Kiernan DP, O'Doherty JV, Sweeney T. (2023) The Effect of Prebiotic Supplements on the Gastrointestinal Microbiota and Associated Health Parameters in Pigs. *Animals*. 13(19):3012.
- Kim HB, Isaacson RE (2015) The pig gut microbial diversity: understanding the pig gut microbial ecology through the next generation high throughput sequencing. *Vet Microbiol* 177:242–51.
- Kim KR, Owens G, Kwon SI, So KH, Lee DB, Ok YS (2010) Occurrence and environmental fate of veterinary antibiotics in the terrestrial environment. *Water Air Soil Poll* 214:163–174.
- Kim HB, Borewicz K, White BA, Singer RS, Sreevatsan S, Tu ZJ, Isaacson RE (2012) Microbial shifts in the swine distal gut in response to the treatment with antimicrobial growth promoter, tylosin. *Proc Natl Acad Sci USA* 109(38):15485–90.
- Kimera, ZI, Mshana SE, Rweyemamu MM, Mboera LEG, Matee MIN (2020) Antimicrobial use and resistance in food-producing animals and the environment: an African perspective. *Antimicrob Resist Infect Control* 9:37.
- Kirchhelle C (2018) Pharming animals: a global history of antibiotics in food production (1935–2017). *Palgrave Commun* 4:96.
- Kongsted H, Pedersen K, Hjulsgaard CK, Larsen LE, Pedersen KS, Jorsal SE, Bækbo P (2018) Diarrhoea in neonatal piglets: a case control study on microbiological findings. *Porcine Health Manag* 4:17.
- Lauridsen C (2020) Effects of dietary fatty acids on gut health and function of pigs pre- and post-weaning. *J Anim Sci* 98(4):skaa086.
- Lekagul A, Tangcharoensathien V, Yeung S (2019) Patterns of antibiotic use in global pig production: a systematic review. *Vet Anim Sci* 7:100058.
- Levin D, Raab N, Pinto Y, Rothschild D, Zanir G, Godneva A, Mellul N, Futorian D, Gal D, Leviatan S, Zeevi D, Bachelet I, Segal E (2021) Diversity and functional landscapes in the microbiota of animals in the wild. *Science*. 372:eabb5352.
- Li J, Yang K, Ju T, Ho T, McKay CA, Gao Y, Forget SK, Gartner SR, Field CJ, Chan CB, Willing BP (2017) Early life antibiotic exposure affects pancreatic islet development and metabolic regulation. *Sci. Rep.* 7:1–12.
- Li Z, Ma Z, Li Y, Gao S, Xiao S (2020) Porcine epidemic diarrhea virus: Molecular mechanisms of attenuation and vaccines. *Microb Pathog* 149:104553.
- Liao SF (2021) Invited Review: Maintain or Improve Piglet Gut Health around Weaning: The Fundamental Effects of Dietary Amino Acids. *Animals* 11:1110.
- Liao SF, Ji F, Fan P, Denryter K (2024) Swine Gastrointestinal Microbiota and the Effects of Dietary Amino Acids on Its Composition and Metabolism. *Int J Mol Sci* 25(2):1237.
- Liu F, Cottrell JJ, Furness JB, Rivera LR, Kelly FW, Wijesiriwardana U, Pustovit RV, Fothergill LJ, Bravo DM, Celi P, Leury BJ, Gabler NK, Dunshea FR (2016) Selenium and vitamin E together improve intestinal epithelial barrier function and alleviate oxidative stress in heat-stressed pigs. *Exp Physiol* 101(7):801–10.
- Liu L, Chen D, Yu B, Yin H, Huang Z, Luo Y, Zheng P, Mao X, Yu J, Luo J (2020) Fructooligosaccharides improve growth performance and intestinal epithelium function in weaned pigs exposed to enterotoxigenic *Escherichia coli*. *Food Funct* 11:9599–9612.
- Liu P, Piao X, Kim S, Wang L, Shen Y, Lee H, Li S (2008) Effects of chito-oligosaccharide supplementation on the growth performance, nutrient digestibility, intestinal morphology, and fecal shedding of *Escherichia coli* and *Lactobacillus* in weaning pigs. *J Anim Sci* 86:2609–2618.
- Liu Q, Gerdt V (2021) Transmissible Gastroenteritis Virus of Pigs and Porcine Epidemic Diarrhea Virus (Coronaviridae). In: *Encyclopedia of Virology*. pp. 850–3.
- Liu Q, Wang HY (2021) Porcine enteric coronaviruses: an updated overview of the pathogenesis, prevalence, and diagnosis. *Vet Res Commun* 45(2-3):75–86.
- Luppi A, Gibellini M, Gin T, Vangroenweghe F, Vandembroucke V, Bauerfeind R, Bonilauri P, Labarque G, Hidalgo A (2016) Prevalence of virulence factors in enterotoxigenic *Escherichia coli* isolated from pigs with post-weaning diarrhea in Europe. *Porcine Health Manag* 2:20.
- Luppi A. (2017) Swine enteric colibacillosis: diagnosis, therapy and antimicrobial resistance. *Porc Health Manag* 3:16.
- Ma Y, Han X, Fang J, Jiang H (2021) Role of dietary amino acids and microbial metabolites in the regulation of pig intestinal health. *Anim Nutr* 9:1–6.
- Liao SF, Ji F, Fan P, Denryter K (2024) Swine Gastrointestinal Microbiota and the Effects of Dietary Amino Acids on Its Composition and Metabolism. *Int J Mol Sci* 25(2):1237.
- Maes D, Vyt P, Rabaey P, Gevaert D (2007) Effects of toltrazuril on the growth of piglets in herds without clinical isosporosis. *Vet J* 173:197–199.
- Maltecca C, Bergamaschi M, Tiezzi F (2020) The interaction between microbiome and pig efficiency: a review. *J Anim Breed Genet* 137:4–13.
- Marthaler D, Rossow K, Culhane M, Collins J, Goyal S, Ciarlet M, Matthijssens J (2013) Identification, phylogenetic analysis and classification of porcine group C rotavirus VP7 sequences from the United States and Canada. *Virology* 446:189–198.
- McClane BA, Robertson SL, Li J (2013) *Clostridium perfringens*, p 465–489. In: Doyle MP, Buchanan RL (eds) *Food Microbiology: Fundamentals and Frontiers*, 4th ed. ASM Press, Washington, DC.
- Mesonero-Escuredo S, Strutzberg-Minder K, Casanovas C, Segalés J (2018) Viral and bacterial investigations on the etiology of recurrent pig neonatal diarrhea cases in Spain. *Porc Health Manag* 4:5.
- Monger XC, Gilbert AA, Saucier L, Vincent AT (2021) Antibiotic Resistance: From Pig to Meat. *Antibiotics* 10:1209.
- Morin M, Magar R, Robinson Y (1990) Porcine group C rotavirus as a cause of neonatal diarrhea in a Quebec swine herd. *Can J Vet Res* 54:385–389.
- Morin M, Turgeon D, Jollette J, Robinson Y, Phaneuf JB, Sauvageau R, Beauregard M, Teuscher E, Higgins R, Larivière S (1983) Neonatal diarrhea of pigs in Quebec: Infectious causes of significant outbreaks. *Can J Comp Med* 47:11–17.
- Muteeb G, Rehman MT, Shahwan M, Aatif M (2023) Origin of Antibiotics and Antibiotic Resistance, and Their Impacts on Drug Development: A Narrative Review. *Pharmaceuticals* 16(11):1615.
- Nadeau E, Fairbrother JM, Zentek J, Belanger L, Tremblay D, Tremblay CL, Rohe I, Vahjen W, Brunelle M, Hellmann K, Cvejic D, Brunner B, Schneider C, Bauer K, Wolf R, Hidalgo A (2017) Efficacy of a single oral dose of a live bivalent *E. coli* vaccine against post-weaning diarrhea due to F4 and F18-positive enterotoxigenic *E. coli*. *Vet J* 226:32–39.
- Nagy J, Bilkei G (2003) Neonatal piglet losses associated with *Escherichia coli* and *Clostridium difficile* infection in a Slovakian outdoor production unit. *Vet J* 166(1):98–100.
- Neuman H, Forsythe P, Uzan A, Avni O, Koren O (2018) Antibiotics

- in early life: dysbiosis and the damage done. *FEMS Microbiol Rev* 42:489–499.
- Pajarillo EAB, Chae JP, Balolong MP, Kim HB, Park C-S, Kang D-K (2015) Effects of probiotic *Enterococcus faecium* NCIMB 11181 administration on swine fecal microbiota diversity and composition using barcoded pyrosequencing. *Anim Feed Sci Technol* 201:80–8.
- Papatsiros G, Billinis C (2012) The prophylactic use of acidifiers as antibacterial agents in swine. In: *Antimicrobial Agents*. London, UK: InTech; 2012.
- Pluske JR, Turpin DL, Kim JC (2018) Gastrointestinal tract (gut) health in the young pig. *Anim Nutr* 4:187–196.
- Post KW, Songer JG (2004) Antimicrobial susceptibility of *Clostridium difficile* isolated from neonatal pigs with enteritis. *Anaerobe* 10:47–50.
- Posthaus H, Kittl S, Tarek B, Bruggisser J (2020) *Clostridium perfringens* type C necrotic enteritis in pigs: diagnosis, pathogenesis, and prevention. *J Vet Diagn Invest* 32(2):203–212.
- Poudel A, Sharma S, Dhital K, Bhandari S, Rajbhandari PG, Napit R, Puri D, Karmacharya DB (2024) Antimicrobial stewardship hindered by inadequate biosecurity and biosafety practices, and inappropriate antibiotics usage in poultry farms of Nepal-A pilot study. *PLoS One*. 19(3):e0296911.
- Rathnayake D, Mun HS, Dilawar MA, Baek KS, Yang CJ (2021) Time for a paradigm shift in animal nutrition metabolic pathway: dietary inclusion of organic acids on the production parameters, nutrient digestibility, and meat quality traits of swine and broilers. *Life* 11:476.
- Rhouma M, Beaudry F, Thériault W, Letellier A (2016) Colistin in pig production: chemistry, mechanism of antibacterial action, microbial resistance emergence, and one health perspectives. *Front Microbiol* 7:1789.
- Rood JI (2016) General physiological and virulence properties of the pathogenic clostridia. In: Uzal FA, Songer JG, Prescott JF, Popoff MR (Eds), *Clostridial Diseases of Animals*. John Wiley & Sons, Inc, Hoboken, NJ, pp. 7–12. <https://doi.org/10.1002/9781118728291.ch2>
- Rood JI, Adams V, Lacey J, Lyras D, McClane BA, Melville SB, Moore RJ, Popoff MR, Sarker MR, Songer JG, Uzal FA, Van Immerseel F (2018) Expansion of the *Clostridium perfringens* toxin-based typing scheme. *Anaerobe* 53:5–10.
- Silva RO, Oliveira C, Guedes R, Lobato F (2015) *Clostridium perfringens*: A review of the disease in pigs, horses and broiler chickens. *Ciência Rural* 45.
- Simjee S, Ippolito G (2022) European regulations on prevention use of antimicrobials from January. *Braz J Vet Med*. 2022 44:e000822. doi: 10.29374/2527-2179.bjvm000822.
- Sjölund M, Zoric M, Wallgren P (2014) Financial impact of disease on pig production. Part III. Gastrointestinal Disorders. In: *Proceedings of 6th European Symposium of Porcine Health Management*; Italy, Sorrento p. 189.
- Soler C, Goossens T, Bermejo A, Migura-García L, Cusco A, Francino O, Fraile L (2018) Digestive microbiota is different in pigs receiving antimicrobials or a feed additive during the nursery period. *PLoS ONE* 13:e197353.
- Song D, Park B (2012) Porcine epidemic diarrhoea virus: a comprehensive review of molecular epidemiology, diagnosis, and vaccines. *Virus Genes* 44:167–175.
- Songer JG, Post KW, Larson DJ, Jost BH, Glock RD (2000) Infection of neonatal swine with *Clostridium difficile*. *Swine Health Prod* 4:185–189.
- Stokstad EL, Jukes TH, Pierce J, Page AC, Franklin AL (1949) The multiple nature of the animal protein factor. *JBC* 180:647–654.
- Su W, Gong T, Jiang Z, Lu Z, Wang Y (2022) The Role of Probiotics in Alleviating Postweaning Diarrhea in Piglets From the Perspective of Intestinal Barriers. *Front Cell Infect Microbiol* 12:883107.
- Szabó C, Kachungwa Lugata J, Ortega ADSV (2023) Gut Health and Influencing Factors in Pigs. *Animals* 13(8):1350.
- Tams KW, Larsen I, Hansen JE, Spiegelhauer H, Strøm-Hansen AD, Rasmussen S, Ingham AC, Kalmar L, Kean IRL, Angen Ø, Holmes MA, Pedersen K, Jelsbak L, Folkesson A, Larsen AR, Strube ML (2023) The effects of antibiotic use on the dynamics of the microbiome and resistome in pigs. *Anim Microbiome* 5(1):39.
- Taylor M, Coop R, Wall R (2016) *Veterinary Parasitology* 4th edn. West Sussex: WileyBlackwell.
- Theil KW, Saif LJ, Moorhead PD, Whitmoyer RE (1985) Porcine rotavirus-like virus (Group B rotavirus): Characterization and pathogenicity for gnotobiotic pigs. *J Clin Microbiol* 21:340–345.
- Thoms U (2012) Between promise and threat. *NTM J Hist Sci Technol Med* 20:181–214.
- Tsekouras N, Athanasakopoulou Z, Diezel C, Kostoulas P, Braun SD, Sofia M, Monecke S, Ehrlich R, Chatzopoulos DC, Gary D, Krämer D, Spyrou V, Christodoulou G, Billinis C, Papatsiros VG (2022) Cross-Sectional Survey of Antibiotic Resistance in Extended Spectrum  $\beta$ -Lactamase-Producing Enterobacteriaceae Isolated from Pigs in Greece. *Animals* 12(12):1560.
- Uzal FA, Navarro MA, Asin J, Boix O, Ballarà-Rodríguez I, Gibert X (2023) Clostridial diarrheas in piglets: A review. *Vet Microbiol* 280:109691.
- Uzal FA, Plattner BL, Hostetter JM (2016) Alimentary System. In: Jubb, Kennedy & Palmer's *Pathology of Domestic Animals*, Volume 2. Elsevier, pp. 1–257.
- Van Boeckel TP, Brower C, Gilbert M, Grenfell BT, Levin SA, Robinson TP, Teillant A, Laxminarayan R (2015) Global trends in antimicrobial use in food animals. *Proc Natl Acad Sci USA* 112(18):5649–54.
- Van Boeckel TP, Glennon EE, Chen D, Gilbert M, Robinson TP, Grenfell BT, Levin SA, Bonhoeffer S, Laxminarayan R (2017) Reducing antimicrobial use in food animals. *Science* 357(6358):1350–1352.
- Van Boeckel TP, Pires J, Silvester R, Zhao C, Song J, Criscuolo NG, Gilbert M, Bonhoeffer S, Laxminarayan R (2019) Global trends in antimicrobial resistance in animals in low- and middle-income countries. *Science* 365(6459):eaaw1944.
- Vancanneyt M, Snauwaert C, Cleenwerck I, Baele M, Descheemaeker P, Goossens H, Pot B, Vandamme P, Swings J, Haesebrouck F, Devriese LA (2001) *Enterococcus villorum* sp. nov., an enteroadherent bacterium associated with diarrhoea in piglets. *Int J Syst Evol Microbiol* 51:393–400.
- Vidal A, Martín-Valls GE, Tello M, Mateu E, Martín M, Darwich L (2019) Prevalence of enteric pathogens in diarrheic and non-diarrheic samples from pig farms with neonatal diarrhoea in the North East of Spain. *Vet Microbiol* 237:108419.
- Vlasova AN, Amimo JO, Saif LJ (2017) Porcine rotavirus: Epidemiology, immune responses and control strategies. *Viruses* 9:48.
- Wang C, Li P, Yan Q, Chen L, Li T, Zhang W, Li H, Chen C, Han X, Zhang S, Xu M, Li B, Zhang X, Ni H, Ma Y, Dong B, Li S, Liu S (2019) Characterization of the Pig Gut Microbiome and Antibiotic Resistome in Industrialized Feedlots in China. *mSystems*. 4(6):e00206-19.
- Wang H, Zhong Z, Luo Y, Cox E, Devriendt B (2019) Heat-stable enterotoxins of enterotoxigenic *Escherichia coli* and their impact on host immunity. *Toxins* 11(1).
- WHO (2001) Food and Agricultural Organization of the United Nations and World Health Organization. Health and nutritional properties of probiotics in food including powder milk with live

- lactic acid bacteria. Available at: [https://www.who.int/foodsafety/publications/fs\\_management/en/probiotics.pdf](https://www.who.int/foodsafety/publications/fs_management/en/probiotics.pdf). Accessed on 25 September 2024.
- WHO (2015) Library cataloguing-in-publication data global action plan on antimicrobial resistance. Available at: [www.paprika-anecy.com](http://www.paprika-anecy.com). Accessed on 13 September 2020.
- WHO (2019) Monitoring and Evaluation of the Global Action Plan on Antimicrobial Resistance. Available at: <https://www.who.int/publications/i/item/monitoring-and-evaluation-of-the-global-action-plan-on-antimicrobial-resistance>. Accessed on 17 February 2022.
- Wilkins LJ, Monga M, Miller AW (2019) Defining Dysbiosis for a Cluster of Chronic Diseases. *Sci Rep* 9:12918.
- Xu C, Kong L, Gao H, Cheng X, Wang X (2022) A Review of Current Bacterial Resistance to Antibiotics in Food Animals. *Front Microbiol* 13:822689.
- Zhang F, Luo S, Gu J, Li Z, Li K, Yuan W, Ye Y, Li H, Ding Z, Song D, Tang Y (2019) Prevalence and phylogenetic analysis of porcine diarrhea associated viruses in southern China from 2012 to 2018. *BMC Vet Res* 15:470.
- Zivkovic B, Migdal W, Radovic C (2011). Prebiotics in nutrition of sows and piglets. *BAH*. 27.