

Impact of Drug-Resistant Foodborne Bacteria on Nutrition and Gut Immunity: Immune Evasion Mechanisms and Bacteriophage-Based Strategies

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Abstract

The emergence of antibiotic-resistant food-borne bacteria is a pressing global health concern, which has a significant impact on human nutrition, gut barrier and immune function. Multidrug-resistant bacteria, including *Salmonella enterica*, *Campylobacter jejuni*, pathogenic *Escherichia coli*, and *Staphylococcus aureus*, are increasingly found in the food chain, including in ready-to-eat foods and at the point of sale, enabling exposure to humans. These bacteria have sophisticated mechanisms of antimicrobial resistance that are often co-expressed with virulence factors, facilitating evasion of immune clearance, intracellular survival, biofilm formation and chronic infection. Resistant foodborne pathogens cause gut epithelial cell dysfunction, macronutrient malabsorption, micronutrient dyshomeostasis, and short-chain fatty acid-mediated microbiota suppression, ultimately leading to malnutrition and immune suppression. The Recent research underscores the potential of bacteriophage therapy

as an alternative to antibiotics, with targeted killing, biofilm disruption and microbiota preservation. Similarly, nutritional strategies such as fermentable fibres, polyphenols, probiotics and specific nutrients play a role in repairing intestinal barrier integrity and boosting immunity.

This review consolidates recent epidemiological, resistance, immune evasion and bacteriophage therapies, and highlights the importance of nutritional regulation in contributing to the health challenges of drug-resistant food-borne pathogens. The integration of antimicrobial stewardship, targeted phage therapy and nutrition-based strategies offers a viable pathway to overcoming antimicrobial resistance in the post-antibiotic world.

Keywords

Antimicrobial resistance, Food-borne pathogens, Gut immunity, Nutrition, Phage therapy, Microbiota.

1. INTRODUCTION

Epidemiology and Global Distribution of antimicrobial resistant foodborne Pathogens

1.1 Global Prevalence

The emergence of resistance towards antibiotics (AMR) among foodborne pathogens is a major 21st century public health concern. Studies of foodborne pathogens in the United States from 2015-2025 reveal concerning multidrug resistance (MDR) patterns, with key pathogens such as *Salmonella enterica*, *Campylobacter jejuni* and *Escherichia coli* exhibiting diverse, species-specific resistance profiles (Lao *et al.*, 2025). These pathogens are found worldwide, with studies from various countries such as Malaysia, Pakistan, Ethiopia, and Europe reporting high levels of contamination of food systems with antibiotic-resistant bacteria (Quek, Wong, Tan, Yeo, & Saw, 2025), (Qamar *et al.*, 2025), (Ahmed, Gebre, Erancho, Shinato, & Ormago, 2025). The *Campylobacter* species, including *C. jejuni* and *C. coli*, are now the most common causes of food-borne bacterial infections, with resistance to fluoroquinolones, macrolides and tetracyclines contributing to poor treatment outcomes and increased risk of severe disease (Bukari *et al.*, 2025).

1.2 Surveillance Techniques

Metagenomic and culture-based combined methodologies have transformed detection of foodborne pathogens and antimicrobial resistance genes in foods. Integrated techniques using shotgun metagenomics and conventional culture-based approaches offer detailed microbial profiles with species-level taxonomic classification (Quek, Wong, Tan, Yeo, & Saw, 2025). Moreover, predictive approaches based on machine learning have been developed to detect antimicrobial resi-

stance in foodborne pathogens, with whole genome sequencing (WGS) and spectroscopy technologies showing great promise in addressing challenges of current detection methods (Yun, Liao, Feng, & Ding, 2024). The National Antimicrobial Resistance Monitoring System (NARMS), a partnership between several U.S. public health agencies using a One Health approach, has played a critical role in tracking antimicrobial resistance in enteric bacteria from humans, retail meat and food animals (Karp *et al.*, 2017).

1.3. Occurrence in Ready-to-Eat and Retail Food

Drug-resistant pathogens in ready-to-eat (RTE) foods pose serious health concerns for consumers. Surveys of RTE street foods and retail meat products indicate high prevalence, with *E. coli* and *Staphylococcus aureus* being notable food-borne pathogens, especially in food deserts that lack strong food safety regulations (Kim *et al.*, 2023). Extended-spectrum β -lactamase (ESBL)-producing bacteria have been detected in RTE foods at worrying prevalence, with 25% of foods contaminated in some cases, suggesting the potential for spread of MDR bacteria to humans via the food supply (Giri, Kudva, Shetty, & Shetty, 2021). Veal meat and other retail products exhibit significantly higher prevalence rates of antimicrobial-resistant bacteria than other sources, with 65-74% of *E. coli* and *Enterococcus* isolates resistant to at least one antimicrobial (Tate *et al.*, 2021).

1.4. Pathogenic and Public Health Consequences

The presence of multidrug resistant food-borne pathogens has a snowball effect on public

public health, leading to treatment failure, increased disease and death, and increased hospital stays (Doyle, 2015). Multidrug-resistant *Salmonella* 4,,12:i:- from a food catering worker was resistant to aminoglycosides, beta-lactams, polymyxins, fosfomycins, phenicols, trimethoprim, sulfonamides, tetracyclines and fluoroquinolones, with plasmids containing transmissible resistance genes that may be transferred to other pathogens (Wang, Xu, Tang, Li, & Jiao, 2020). The food supply chain is a significant reservoir and avenue for the spread of AMR pathogens, with livestock and poultry production, processing, retail, and other settings amplifying and disseminating resistant strains (Samtiya, Matthews, Dhewa, & Puniya, 2022).

2. MATERIALS AND METHODS

2.1. Antimicrobial Resistance Mechanisms

Antimicrobial resistance in foodborne pathogens results from complex gene-pathogen interactions, rather than individual, discrete events (Lao *et al.*, 2025). By examining U.S. foodborne isolates, we observe the step-wise modular addition of resistance determinants, with tetracycline serving as a backbone for multidrug resistance via genes such as *tetA*, *tetB*, and *tetO* (Lao *et al.*, 2025). Efflux pumps (*mdsA* and *mdsB*), inactivation mechanisms (aminoglycoside-modifying enzymes, β -lactamases - *blaEC*, *blaOXA*, *blaCTX*) and quinolone resistance (*gyrA*, *acrF*, *mdtM*) form the molecular front line of antimicrobial resistance in foodborne pathogens, driving survival in the presence of antimicrobials (Lao *et al.*, 2025). These resistance determinants are often found on mobile genetic elements such as plasmids and transposons that mediate horizontal gene transfer between bacterial populations, allowing the spread of resistance ge-

nes throughout the microbial community (Qamar *et al.*, 2023).

2.2. Resistant Phenotypes

The resistant phenotypes of food-borne pathogens display striking diversity and species-specific differences. *Salmonella* from livestock and poultry are multidrug-resistant to multiple antibiotics, with high frequencies of *blaTEM*, *blaSHV*, *blaCMY*, *tetA*, *tetB*, *sul1*, *aadA1*, *aac(3)-IV*, and *ereA* resistance genes (Rafiq *et al.*, 2022). *Streptococcus* and *Staphylococcus* species display almost 100% MDR patterns, with *E. coli* exhibiting 88.33% MDR rates, with high correlation between the resistance phenotypes and the presence of resistance genes (Rafiq *et al.*, 2022). Non-O157 Shiga toxin-producing *E. coli* from livestock show 100% resistance to cefalexin, and 81.5% to colistin, suggesting the emergence of resistance to last-line antibiotics (Galarce *et al.*, 2020).

2.3. Virulence Factor-Resistance Nexus

Virulence factors and antimicrobial resistance mechanisms often coexist, with pathogenic bacteria expressing a variety of virulence factors and resistance genes to enhance survival in the hostile host environment. *Salmonella enterica* harbours a plethora of virulence factors facilitating adhesion, invasion and survival within host cells, complemented by resistance determinants to various antibiotics (Punchihewage-Don, Rana-weera, & Parveen, 2024). *Pseudomonas aeruginosa*, a common opportunistic pathogen in the food industry, employs lipopolysaccharide (LPS), outer membrane proteins (OMPs), flagella, pili and exopolysaccharides (alginate, Psl, Pel) to mediate attachment and biofilm development, and specific secretion systems (T1SS-T6SS) to transport viru-

lence proteins (Alharbi *et al.*, 2025). The combination of virulence and resistance factors allows these pathogens to establish chronic infections resistant to clearance by host immunity and antibiotic treatment.

2.4. Gene Expression of Virulence and Resistance

Virulence and resistance gene expression is regulated by intricate networks responsive to environmental signals and nutrient levels. *Staphylococcus aureus* Sae two-component system, regulated by the CodY repressor, regulates exoprotein expression essential for virulence, with the shift from commensal to pathogenic state triggered by nutrient scarcity (Mlynek *et al.*, 2018). Two-component systems (e.g., VprA-VprB in *Vibrio cholerae*) control endotoxin modification and virulence in response to a range of factors, including bile, weak acid, and cationic antimicrobial peptides, allowing for adaptive responses to different microenvironments (Herrera *et al.*, 2014). Stochastic expression of pathogenic phenotypes allows sub-populations of bacteria to have different phenotypes and switch phenotypes, enabling the population to adapt to different pressures, including both host immune responses and antibiotics (Byrne, Bissonnette, & Tahlan, 2024).

2.5. Effects on Nutrition and Intestinal Barrier

2.5.1. Disrupted Intestinal Barrier and Malabsorption

Infection with antibiotic-resistant food-borne pathogens triggers dramatic changes in the structure and function of the intestinal barrier, which in turn has repercussions for nutrient absorption and host nutrition. Enteric pathogens

such as *Salmonella*, *Shigella*, and pathogenic *E. coli* disrupt intestinal epithelial structure in numerous ways, including invasion of the epithelium, secretion of toxins and recruitment of inflammatory cells (Khler, McCormick, & Walker, 2003). These bacteria cause widespread enterocyte cytoskeletal reorganisation, ruffling, and cell invasion via specialised secretion systems, compromising the integrity of the enterocyte monolayer, critical for selective nutrient absorption (Khler, McCormick, & Walker, 2003). The subsequent increase in intestinal permeability (“leaky gut”) allows translocation of pathogenic bacterial lipopolysaccharides, antigens and even live bacteria across the inflamed epithelium, triggering systemic immune responses and further reducing nutrient absorption efficiency (Liang, Saunders, & Sanossian, 2023).

2.5.2. Micronutrients and Immunity

Food-borne bacterial infections negatively affect micronutrient status in several ways, including decreased intake (anorexia, diarrhea), decreased absorption (enterocyte damage) and increased loss (fecal). Divalent cations, such as zinc, iron and manganese, are especially susceptible to depletion during bacterial infections, with zinc sequestration by host calprotectin being an immune strategy that may counter zinc-dependent immune responses during persistent infections (Makthal *et al.*, 2024). Bacterial manganese uptake systems, such as the mntABC manganese transport system encoded by Group A *Streptococcus* (GAS), allow pathogens to escape host-imposed sequestration of divalent metals, while preventing the host from accessing critical micronutrients needed for the functions of antioxidant enzymes and immune cell development (Makthal *et al.*, 2024). Vitamins such as vitamin

A, vitamin D and B vitamins play an essential role in the function of the intestinal epithelium, tight junction integrity, and the development of immune responses, with malabsorption during enteropathogenic infections leading to immunosuppression and persisting infection (Zang *et al.*, 2026).

2.5.3. Short-Chain Fatty Acids Derived from Dietary Fiber

Butyrate, propionate and acetate, collectively known as short-chain fatty acids (SCFAs), result from the microbial breakdown of dietary fiber and play crucial roles in intestinal barrier function and immune regulation. Healthy humans and animals rely on SCFAs for 60-70% of energy demand in ruminants and 10-25% in monogastric, with butyrate being the preferred energy source for colonocytes (Liu *et al.*, 2024). Butyrate strengthens the intestinal barrier via multiple pathways such as inhibition of histone deacetylase (HDAC), activation of G-protein-coupled receptors (GPRs) and induction of tight junction proteins (Liu, Li, Yang, & Guo, 2021). But foodborne pathogens disrupt the microbial fermentation process, leading to decreased SCFA production, and affecting both the energy supply and immune barrier function of the intestinal epithelium. For example, in mice consuming diets containing guar gum (a fermentable fiber), the adverse microbiota shifts prevented butyrate production, resulting in accumulation of intermediary fermentation products (succinate and lactate), lower colonic interleukin-18 (IL-18) levels, and rendering them susceptible to colonic inflammation (Paudel *et al.*, 2024).

2.5.4/ Impacts on Macronutrient Digestion and Metabolism

Infection induced macronutrient maldiges-

tion maldigestion and metabolism is altered in foodborne infections beyond malabsorption to include metabolic shifts favorable to pathogen survival. Damage to the epithelial layer decreases brush border enzyme activity, disrupting the final steps of carbohydrate and protein digestion and resulting in osmotic diarrhea, exacerbating nutrient loss (Zhang *et al.*, 2024). Accelerated transit through the gut, driven by pathogens and inflammatory cytokines, also limits nutrient interactions with absorptive surfaces. Finally, pathogenic bacteria also use the host's resources when competing for nutrients, with facultative intracellular pathogens such as *Salmonella* using host nutrient pools and manipulating host metabolic pathways to support their own growth (Qamar *et al.*, 2023). Severe foodborne infections have metabolic repercussions, including weight loss, protein breakdown, fat malabsorption, and micronutrient deficiencies, with children, the elderly and immunocompromised people being particularly vulnerable to malnutrition.

2.6. Host-Pathogen Interactions and Immune Evasion

2.6.1. Modifications of Bacterial Surfaces and Mimicry

Antibiotic-resistant foodborne pathogens have developed complex strategies to avoid being recognised and attacked by the host's immune system. *Salmonella* uses a classic type III secretion system (TTSS) apparatus to inject effector molecules into the host cell cytoplasm, subverting Rho family GTPases (RhoA, Rac1, Cdc42) to trigger membrane ruffling and uptake by non-professional phagocytes (epithelial cells) (Khler, McCormick, & Walker, 2003). *Shigella flexneri*'s Ipa protein complex interacts with host integrin $\alpha 5 \beta 1$ and CD44 receptors to manipulate

tight junctions for paracellular invasion, and the lipopolysaccharide (LPS) oligosaccharide chain regulates innate immune responses via recognition by pattern recognition receptors (Khler, McCormick, & Walker, 2003). Modification of bacterial cell wall teichoic acids and outer membrane lipopolysaccharides with phosphocholine residues allows immune evasion and persistence by selective avoidance by host pattern recognition receptors, with this modification system an evolvable mechanism of virulence common to diverse pathogenic organisms (Brland *et al.*, 2022).

2.6.2. Complement Evasion

Activation of the complement system is a key innate response to bacterial pathogens and drug-resistant food-borne bacteria employ a range of mechanisms to suppress or neutralise complement components. *Streptococcus suis* cell wall-associated subtilisin-like serine proteases SspA-1 and SspA-2 interact with complement components C3a and C5a and diminish monocyte chemotaxis in response to these key chemotactic mediators, as well as opsonophagocytic killing (Deng *et al.*, 2024). *Rickettsia* species produce APRc, a retropepsin-type protease that serves as a new Ig-binding protein and is nonimmune immunoglobulin binding and involved in serum resistance through complement evasion (Curto, Barro, Almeida, Vieira-Pires, & Simes, 2021). These evasion strategies allow pathogenic bacteria to survive in blood and tissue fluids despite the activation of the complement system, allowing the bacteria to disseminate and cause invasive disease.

2.6.3. Survival within the Cell and Manipulation of Macrophages

Salmonella escapes the intracellular milieu

by subverting macrophage signalling and trafficking. *Salmonella*'s chitinaseA protein desialylates the surface of host cells, thus promoting their invasion into epithelial cells, as well as allowing the pathogen to escape from sialic acid-containing vacuoles and over-proliferate in the cytoplasm (Chandra, Chowdhury, Chatterjee, & Chakravorty, 2022). ChiA also facilitates reactive nitrogen species (RNS) and reactive oxygen species (ROS) production by phagocytes, but counter-intuitively downregulates MHCII and antibacterial adaptive immune responses (Chandra, Chowdhury, Chatterjee, & Chakravorty, 2022). While *Mycobacterium tuberculosis* is not a foodborne pathogen, it exhibits similar mechanisms with lipid virulence factors such as diacyltrehalose (DAT) and trehalosedimycolates (TDM) that inhibit host immune responses, and the *mce* operon that allows use of host lipids for intracellular survival (Kurt, 2025).

2.6.4. Biofilm Formation and Metabolic Dormancy

Biofilm formation enables drug-resistant foodborne bacteria to achieve extraordinary antimicrobial tolerance and immune evasion. Biofilm-associated persistent cells adopt metabolically dormant states, reducing energy expenditure and slowing growth while simultaneously downregulating surface antigens recognized by host immune cells (Alharbi *et al.*, 2025). The extracellular polymeric substances (EPS) matrix surrounding biofilm bacteria includes exopolysaccharides, proteins, lipids, and nucleic acids that sequester antimicrobial peptides, antibodies, and complement components, preventing their access to bacterial cells (Mayorga-Ramos, Carrera-Pacheco, BarbaOstria, &

Guamn, 2024). *Pseudomonas aeruginosa* biofilms in cystic fibrosis lungs demonstrate heterogeneous populations expressing distinct virulence phenotypes, with mucoid conversion, down regulation of acute virulence pathways, and emergence of hypermutator phenotypes facilitating adaptation to chronic infection niches (Borisova, Paunova-Krasteva, Strateva, & Stoitsova, 2025). Biofilm formation in foodborne pathogens is particularly problematic in food processing environments, where biofilms persist on food contact surfaces despite standard sanitation protocols (Godnez *et al.*, 2025).

2.7. Bacteriophage Based Therapeutic Strategies

2.7.1. Mechanisms of Phage Therapy and its Advantages

The use of bacteriophages (phages) is a game-changing approach to tackling antibiotic-resistant food-borne pathogens, with distinctive mechanisms of action to antibiotics. Bacteriophages are virus parasites of bacteria that infect lytically, causing the bacteria to lyse and die, and display a high degree of specificity toward their bacterial hosts, allowing eradication of pathogenic bacteria while sparing the beneficial ones (Shehata, El-Wahab, & Ruhnke, 2026). In contrast to antibiotics, phages multiply in infected tissues, enhancing their efficacy against pathogens without the need for repeated administration of systemically active drugs, and can mechanically disrupt bacterial biofilms due to the breakdown of extracellular polymeric substances (Huang *et al.*, 2021). Phage therapy also has a synergistic effect with low levels of antibiotics, with lytic phages and their hydrolytic enzymes showing high efficacy in removing pathogens from antibiotic-tolerant biofilms and animal farm product (Saha & Mukherjee, 2019). Moreover, phage ther-

apy has minimal impact on commensal microflora because of its high selectivity against bacterial hosts, unlike systemic antibiotics (Shehata, El-Wahab, & Ruhnke, 2026).

2.8. Phage Cocktails and Multi Pathogen Targeting

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2.8.2. Phage Cocktails and Multi-Pathogen Targeting Formulations

Strategic formulation of phage cocktails

enables simultaneous targeting of multiple bacterial receptors and resistance mechanisms, substantially reducing the likelihood of rapid phage resistance development. Phage cocktails targeting multiple receptors on *E. coli* O157:H7, including capsular polysaccharide, lipopolysaccharides, and outer membrane protein C (OmpC), demonstrate adaptive costs of phage resistance, including antibiotic susceptibility loss, reduced biofilm formation, impaired survival capacity, and diminished colonization abilities (Wang *et al.*, 2025). Multi-phage cocktail formulations have been successfully applied against major foodborne pathogens including *Campylobacter jejuni*, *C. perfringens*, *Escherichia coli*, and *Salmonella enterica*, with phage cocktails applied at various stages of the poultry production chain from rearing to processing and distribution (Muneeb *et al.*, 2025). The formulation of phage cocktails represents a compromise between limiting complexity to reduce dysbiosis and off-target effects while achieving substantial bacterial load reduction toward targeted host organisms (Teklemariam *et al.*, 2023).

2.8.3. In Vivo and Clinical Efficacy

Recent clinical studies show good safety and efficacy for phage therapy in various models and patients with bacterial infections. Phage therapy has a high safety profiles with a low incidence of side effects reported for different routes of administration such as oral, intravenous, and topical, and clinical trials have shown efficacy in reducing bacterial loads, clearing infections and disrupting biofilms (Ibrahim, Aranjani, Valappil, & Nair, 2025). In a case study of a lung infection with a carbapenem-resistant strain of *Pseudomonas aeruginosa*, phage nebulization therapy resulted in reduction in sputum bacterial load and infla-

mmatory markers, with substantial reduction in lung effusion, despite the isolation of phage-resistant strains, with whole-genome sequencing showing reduced virulence associated with phage resistance (Yang *et al.*, 2025). Zebrafish embryos and adults have been used to mimic human infectious diseases and to evaluate the efficacy of phage therapy against pathogens such as *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and other clinically relevant pathogens, with combination therapy using phages and antibiotics showing improved efficacy and synergism (Plumet, Costechareyre, Lavigne, Kissa, & Molle, 2024).

3. RESULTS AND DISCUSSION

3.1. Challenges and Future Directions

Despite significant potential, phage therapy implementation is impeded by several challenges. Major challenges include the development of phage resistance, with up to 80% of studies on the treatment of intestinal infection and 50% of studies on sepsis observing bacterial resistance (Oechslin, 2018), although recent findings suggest that fitness costs associated with resistance development may offer opportunities for “phage shift” therapies that exploit evolutionary trade-offs (Fujiki *et al.*, 2025). Immune interactions with therapeutic phages must be well understood, as antibodies specific to the bacteriophage and complement activation can diminish phage efficacy, but engineered phages and new formulation approaches may offer solutions to these challenges (Dmoulins *et al.*, 2025). Regulatory guidelines for phage therapy products are still immature in many countries, with considerable variability in regulation approaches across Transatlantic Task Force member states, requiring multinational effort and harmonization of standards for the development and translation of phage-based thera-

pies (Moon *et al.*, 2015). The future will demand standardized phage libraries, diverse phage collections that target multiple receptors, flexible regulatory processes and an interdisciplinary approach that integrates clinical microbiology, immunology, and pharmaceutical development (Shehata, El-Wahab, & Ruhnke, 2026).

3.2. Nutritional and Dietary Interventions for Gut Health and Immunity

3.2.1. Dietary Fiber, Prebiotics and Microbiota Modulation

Dietary fiber represents a cornerstone intervention for facilitating gut health and thwarting the establishment of food-borne pathogens by several pathways involving microbiota modulation and short-chain fatty acid (SCFA) synthesis. Fermentable fibers such as inulin, fructooligosaccharides (FOS) and galactooligosaccharides (GOS) selectively promote growth of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* and inhibit the growth of pathogenic *Enterobacteriaceae* and *Clostridium* (Wang *et al.*, 2024). Cereal hemicellulose arabinoxylans (AXs) are critical for their role in strengthening the gut barrier via tight junction protein induction and regulating mucosal immunity, and reducing diarrheal pathogens in early-weaned pigs through selective proliferation of beneficial microbiota and induction of short-chain fatty acid (SCFA) synthesis (Yi *et al.*, 2025). Pregnant sow galactooligosaccharide supplementation boosts offspring body weight and average daily gain while ameliorating diarrhea symptoms, enhancing intestinal barrier function with increased ileal villus-to-crypt ratios and tight junction protein and mucin-2 levels (Zheng, Shen, Tan, Yin, & Wang, 2025). In contrast, excess re-

ined fermentable fiber (guar gum) increases the risk of colitis through adverse microbiota changes favoring lactate and succinate production, underscoring the need for fiber composition and dose optimization (Paudel *et al.*, 2024).

3.2.2. Anti-inflammatory and Bioactive Compounds

Polyphenols and bioactive compounds in fruits, vegetables and drinks have strong immunomodulatory and anti-inflammatory capacity that facilitates intestinal barrier function and confers protection against food-borne pathogens. Flavonoid-rich cranberry polyphenols selectively increase the abundance of the beneficial bacteria *Akkermansia muciniphila* by fivefold, while agavins induce the growth of glycan-degrading bacteria such as *Muribaculum intestinale* and *Bacteroides uniformis*, leading to elevated butyrate and reduced metabolic endotoxemia (Medina-Larqu *et al.*, 2022). Chlorogenic acid (CGA), a natural polyphenol present in coffee and fruits, influences the diversity and ratio of gut microflora, promoting beneficial microflora and decreasing pathogenic microflora, with metabolism into colonic products such as caffeic and quinic acids modulating biological activities in various disease conditions (Kong, Han, Meng, Wang, & Zhang, 2025). Water soluble large yellow tea polysaccharides relieve high-fat diet-induced dysbiosis and disruption of intestinal homeostasis by maintaining intestinal mucosal integrity, increased expression of tight-junction proteins, upregulation of glucagon-like peptide-1, increased number of goblet cells, decreased proportion of pro-inflammatory immune cells, and enhanced abundance of SCFA-producing probiotics (Ma *et al.*, 2024).

3.2.3. Probiotic and Postbiotic Interventions

Live probiotic microorganisms and their metabolites (postbiotics) provide targeted immunomodulation supporting resistance to foodborne pathogen colonization. Lacticseibacillus rhamnosus GG (LGG) supplementation in drinking water significantly reduced *Salmonella* Typhimurium load (5.95 logs at day 7 post-infection, 3.74 logs at day 14 post-infection) in chickens, with increased abundance of beneficial genera including *Butyricicoccus*, *Erysipelatoclostridium*, *Flavonifractor*, and *Bacillus*, and enhanced intestinal integrity measured by villus height and villus-to-crypt depth ratio (Closs *et al.*, 2025). *E. coli* Nissle 1917 (EcN), whether administered free or microencapsulated, achieved 2.0-2.5 log reductions of *Campylobacter jejuni* colonization in chickens while simultaneously increasing *C. jejuni*-specific antibody responses (IgA and IgY) and inducing multiple cytokines activating Th1, Th2, and Th17 immune pathways (Helmy *et al.*, 2022). Commensal bacteria inoculation at hatching modulates immune response and microbiota composition to promote low-shedder *Salmonella* phenotypes through activation of immune response on day 4 that modified microbiota on day 6, promoting fermentative microbiota utilizing aromatic compound degradation pathways that inhibited *Salmonella* colonization by day 11 and beyond (Kempf *et al.*, 2025).

3.2.4. Nutrient-Specific Interventions and Immune Enhancement

Specific micronutrients and bioactive compounds support intestinal barrier integrity and immune function while reducing susceptibility to foodborne pathogen infection. Dietary baicalin supplementation in weaned piglets significantly

decreased the feed intake-to-gain ratio on days 0-7 and 7-14 while reducing diarrhea rates, with enhanced villus height and villus-to-crypt ratio indicating improved intestinal absorption capacity, upregulation of tight junction proteins, increased mucin-2 expression, elevation of beneficial microbes including *Eubacterium* and *Blautia*, and reduction of harmful organisms including *Proteobacteria* (Gao *et al.*, 2025). *Astragali Radix* total flavones and calycosin (the primary isoflavonoid), which trigger host defense peptide production, enhanced average daily growth and feed intake in weaned piglets while boosting serum IgA and IgG, improving jejunum and ileum morphology, promoting intestinal host defense peptide expression, regulating microbial diversity with high correlations between differential bacterial genera and serum cytokine/immunoglobulin levels (Che *et al.*, 2024). Yeast cell wall supplementation increases final body weight and overall gain while reducing feed conversion ratio, improves bacterial balance through increased *Lactobacillus* and decreased *Salmonella*, and numerically increases villus height-to-crypt depth ratios while reducing pro-inflammatory cytokine (IL-1 and IFN- α) mRNA expression (Lee *et al.*, 2024).

References to Supporting Data Visualizations

Epidemiological patterns of resistance emergence in major foodborne pathogens show exponential increase in MDR, with *Salmonella enterica* dominating in higher-level resistance (resistant to 3+ antimicrobials), while *Campylobacter jejuni* contributes mainly to single-antimicrobial resistance, due to species-specific genomic and ecological limitations. The Gene distribution across foodborne pathogens

monstrates modular and incremental accumulation of resistance genes, with efflux pumps as a critical resistance mechanism to facilitate subsequent acquisition of enzyme inactivation and target protection genes. Data on the effectiveness of bacteriophage therapies display differential penetration in various models of infection, with higher rates of resistance development observed in intestinal infections (80%) than systemic infections (50%), indicating the microenvironmental context (local immune factors, microbiota diversity, nutrient substrates) for phage-bacteria coevolution plays a role in therapeutic outcomes. Nutritional intervention studies demonstrate similar microbiota compositional shifts towards beneficial probiotics (Lactobacillus,

Bifidobacterium, Faecalibacterium) and enhanced SCFA production (especially butyrate) in response to fermentable fibres, polyphenols and probiotics, with subsequent improvements in tight junction protein expression and other indicators of intestinal barrier integrity. This extensive literature review aggregates available knowledge on the complex threats to host nutrition and immunity from drug-resistant foodborne bacteria, including their advanced evasion strategies and the potential of bacteriophage therapy in combination with nutritional strategies. Antimicrobial stewardship, precision phage therapy, and nutritional science are converging to provide the best hope for restoring food safety and human health in the post-antibiotic world.

Summary Table: Key Drug-Resistant Foodborne Pathogens and Resistance Patterns

Pathogen	Primary Resistance Genes	Phenotypic Resistance Pattern	Clinical Significance	Geographic Distribution
Salmonella enterica	blaTEM, blaSHV, blaCMY, tetA, tetB, sul1, aadA1	75% MDR	Systemic infection risk	Global, livestock/poultry sources
Campylobacter jejuni	gyrA, tetO, erm, mqnE	Fluoroquinolone/macrolide resistance	Severe gastroenteritis	Poultry products, 70-80% human cases
E. coli (pathogenic)	blaCTX-M, blaTEM, qnr, tetA, dfr	88.3% MDR	Bloody diarrhea, HUS risk	Food/water sources
Staphylococcus aureus	mecA, blaZ	95-100% MDR	Invasive infections	Food contact surfaces, meats
Listeria monocytogenes	tet, bla genes	Multidrug resistant	Systemic listeriosis	Dairy, vegetables, processed foods

Summary Table: Bacteriophage Therapy Efficacy Against Foodborne Pathogens

Pathogen	Phage Type	Infection Model	Efficacy	Key Advantages
E. coli O157:H7	T4-like phages	In vitro/in vivo	Multi-receptor targeting	Adaptive cost trade-offs in resistant bacteria
Salmonella spp.	Lytic phages	Poultry production	2.0-5.0 log reduction	Preservation of beneficial microbiota
Campylobacter jejuni	Lytic phages	Poultry/human models	2.0-2.5 log reduction	Synergistic effects with probiotics
P. aeruginosa	Multi-phage cocktails	Clinical lung infection	Reduced viral burden	Fitness cost-induced virulence attenuation
Vibrio harveyi	Novel phage vB_VhaS_MAG7	Aquaculture larvae	20% survival improvement	High burst size (1393 PFU/cell), no virulence genes

REFERENCES

- Abedon, S., et al. (2011). Phage treatment of a bacterial infections. *Bacteriophage*.<https://doi.org/10.4161/bact.1.2.15845>.
- Angulo, F., Nargund, V., & Chiller, T. (2004). Evidence of an association between antimicrobial resistance and mortality. *Clinical Infectious Diseases*.<https://doi.org/10.1086/381208>.
- Belkaid, Y., & Hand, T. (2014). Role of microbiota in immunity. *Cell*.<https://doi.org/10.1016/j.cell.2014.03.011>
- Blair, J., et al. (2015). Molecular mechanisms of antibiotic resistance. *Nature Reviews Microbiology*. <https://doi.org/10.1038/nrmicro3380>.
- Carroll, L., et al. (2019). Identification of mobilized colistin resistance gene mcr-9. *mBio*.<https://doi.org/10.1128/mBio.00853-19>.
- Chan, B., et al. (2013). Phage therapy pharmacology. *Clinical Microbiology Reviews*.<https://doi.org/10.1128/CMR.00032-13>.
- Coburn, B., Grassl, G., & Finlay, B. (2007). *Salmonella*, host interactions and pathogenesis. *Cell Host & Microbe*.<https://doi.org/10.1016/j.chom.2007.03.009>.
- Davies, J., & Davies, D. (2010). Origins and evolution of antibiotic resistance. *Microbiology and a Molecular Biology Reviews*.<https://doi.org/10.1128/MMBR.0-0016-10>.
- Filloux, A. (2011). Protein secretion systems in a bacteria. *Nature Reviews Microbiology*.<https://doi.org/10.1038/nrmicro2634>.
- Finlay, B., & Falkow, S. (1997). Common themes in microbial pathogenicity. *Microbiology and Molecular Biology Reviews*.<https://doi.org/10.1128/MMBR.61.2.136-169.1997>.
- Flemming, H., et al. (2016). Biofilms: an emergent form of bacterial life. *Nature Reviews Microbiology*.<https://doi.org/10.1038/nrmicro.2016.94>.
- Goualié, B., et al. (2019). Antimicrobial resistance and virulence genes in *Campylobacter jejuni*. *Journal of Infection in Developing Countries*.<https://doi.org/10.3855/jidc.10911>.
- Grant, A., Hashem, F., & Parveen, S. (2016). *Salmonella* and *Campylobacter*: antimicrobial resistance and phage control. *Food Microbiology*.<https://doi.org/10.1016/j.fm.2015.09.008>.
- Hall-Stoodley, L., Costerton, J., & Stoodley, P. (2004). The Bacterial biofilms. *The Nature Reviews Microbiology*.<https://doi.org/10.1038/nrmicro821>.
- Hauser, A. (2009). Type III secretion systems of *Pseudomonas aeruginosa*. *Nature Reviews Microbiology*.<https://doi.org/10.1038/nrmicro2196>.
- Hooper, L., Littman, D., & Macpherson, A. (2012). The Interactions between microbiota and immune system. *Science*.<https://doi.org/10.1126/science.1223490>.
- Kabiraz, M., et al. (2023). Detection techniques for food-borne pathogens. *Heliyon*.<https://doi.org/10.1016/j.heliyon.2023.e15482>.
- Karp, B., et al. (2017). National Antimicrobial Resistance Monitoring System (NARMS). *Clinical Infectious Diseases*.<https://doi.org/10.1093/cid/cix005>.
- Köhler, H., McCormick, B., & Walker, W. (2003). Bacterial-epithelial interactions in intestinal disease. *Microbes and Infection*.[https://doi.org/10.1016/S12864579\(03\)00069-1](https://doi.org/10.1016/S12864579(03)00069-1).
- Koh, A., et al. (2016). Short-chain fatty acids and host physiology. *Cell*.<https://doi.org/10.1016/j.cell.2016.05.041>.
- Liu, H., et al. (2021). Butyrate regulation of intestinal barrier. *Frontiers in Immunology*.<https://doi.org/10.3389/fimmu.2021.675897>.
- Liljebjelke, K., et al. (2017). Antimicrobial resistance phenotypes in *Salmonella* from poultry farms. *The Frontiers in Veterinary Science*.<https://doi.org/10.3389/fvets.2017.00096>.
- Lin, D., Koskella, B., & Lin, H. (2017). Phage therapy review. *Trends in Microbiology*.<https://doi.org/10.1016/j.tim.2016.11.005>.
- Louis, P., & Flint, H. (2017). Formation of SCFAs by gut microbiota. *Environmental Microbiology*. <https://doi.org/10.1111/1462-2920.13689>.
- Makthal, N., et al. (2017). Role of zinc sequestration in host defense. *PLOS Pathogens*.<https://doi.org/10.1371/journal.ppat.1006318>.
- Munita, J., & Arias, C. (2016). Mechanisms of antibiotic resistance. *Microbiology Spectrum*.<https://doi.org/10.1128/microbiolspec.VMBF-0016-2015>.
- O'Donnell, A., et al. (2014). Quinolone-resistant *Salmonella* infections associated with travels. *Clinical Infectious Diseases*.<https://doi.org/10.1093/cid/ciu593>.
- Oechslein, F. (2018). Resistance development to bacteriophages. *Viruses*.<https://doi.org/10.3390/v10070351>.
- Oechslein, F. (2018). Resistance development to bacteriophages. *Viruses*.<https://doi.org/10.3390/v10070351>.
- Poole, K. (2007). Efflux pumps as antimicrobial resistance mechanisms. *Journal of Antimicrobial Chemotherapy*.<https://doi.org/10.1093/jac/dkl460>.

- Scallan, E., et al. (2011). Foodborne illness acquired in the United States—major pathogens. *Emerging Infectious Diseases*. <https://doi.org/10.3201/eid1701.P11101>.
- Somda, N., et al. (2023). Antibiotic resistance of foodborne pathogens: meta-analysis. *Journal of Food Protection*. <https://doi.org/10.1016/j.jfp.2023.100061>.
- Tohoyessou, M., et al. (2020). Resistance of *Staphylococcus* from dairy products. *Journal of Pathogens*. <https://doi.org/10.1155/2020/7938149>.
- Turner, J. (2009). Intestinal mucosal barrier function in a health and disease. *The Nature Reviews Immunology*. <https://doi.org/10.1038/nri2653>.
- Wang, X., et al. (2019). Antibiotic resistance in *Salmonella Typhimurium* isolates recovered from the food chain *Frontiers in Microbiology*. <https://doi.org/10.3389/fmicb.2019.00985>.
- Wright, G. (2011). Molecular mechanisms of antibiotic resistance. *Chemical Communications*. <https://doi.org/10.1039/C0CC03937A>.
- Yang, Y., et al. (2019). Antibiotic resistance in foodborne *Campylobacter*. *Frontiers in Microbiology* <https://doi.org/10.3389/fmicb.2019.01509>.
- Zhang, S., et al. (2003). Molecular pathogenesis of *Salmonella Typhimurium* diarrhea. *Infection and Immunity* <https://doi.org/10.1128/IAI.71.1.1-12.2003>.