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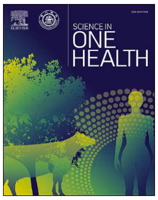

Review

Antimicrobial resistance in *Salmonella*: One Health perspective on global food safety challenges

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ABSTRACT

Antimicrobial resistance (AMR) in *Salmonella* is a major concern in terms of human health, environmental sustainability, and global food security. *Salmonella*, the world's most prevalent foodborne pathogen, has gradually gained resistance to important drugs, complicating treatment efforts and leading to rising morbidity, mortality, and economic costs. Overuse of antibiotics in human medicine and agriculture, inadequate regulatory compliance, and environmental pollution from agricultural runoff and treated sewage all contribute to the growth and spread of AMR in *Salmonella*. Health as well as viewpoints on environmental, animal, and human health will be required to address this complicated problem. This includes promoting reasonable antibiotic use, improving global surveillance systems, and researching novel treatments including phage therapy, probiotics, and new antibiotics. Proposals for vaccination and precise food safety standards are critical for limiting *Salmonella* transmission across the food chain. Despite significant progress, critical research gaps continue, specifically in understanding the molecular basis of resistance and the role of environmental practices. However, contemporary research endeavors are concentrated on identifying and comprehending the prevalence of extensively drug-resistant *Salmonella* strains, elucidating the bacterium's defense mechanisms against antibiotics, and investigating outbreaks associated with vegetables. Global surveillance, the development of alternative therapies, and the implementation of stricter antibiotic policies are essential strategies in addressing AMR in *Salmonella*. Additionally, policy design and implementation, capacity building in low- and middle-income countries, and raising public awareness all necessitate urgent global collaboration among governments, international agencies, non-governmental organizations, and the corporate sector. Stricter regulations on overuse of antibiotics in agriculture is also called for. This review highlights the importance of multi-disciplinary struggles in engaging *Salmonella*, as integrated resolutions through a One Health approach are crucial for ensuring food safety, preserving public health, and minimizing the worldwide threat of AMR.

Abbreviations: WHO, World Health Organization; NTS, non-typhoidal *Salmonella*; LMICs, low- and middle-income countries; AMR, antimicrobial resistance; MDR, multi-drug resistant; HGT, horizontal gene transfer; ESBLs, extended-spectrum β-lactamases; MGEs, mobile genetic elements; LPS, lipopolysaccharide; PBPs, penicillin-binding proteins; AMEs, aminoglycoside-modifying enzymes; KPC, *Klebsiella pneumoniae* carbapenemases; MBL, metallo-β-lactamase; GLASS, Global Antimicrobial Resistance Surveillance System; AMPs, antimicrobial peptides; EARS-Net, European Antimicrobial Resistance Surveillance Network; NARMS, U.S. National Antimicrobial Resistance Monitoring System; EFSA, European Food Safety Authority; MEV, meropenem–vaborbactam; ICR, imipenem–cilastatin/relebactam.

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1. Introduction

Salmonella is a gram-negative, rod-shaped facultatively anaerobic bacterium belonging to the Enterobacteriaceae family that causes foodborne infections in humans and animals [1,2] It is an opportunistic organism isolated from a wide variety of soils, water, and animal and human digestive systems [3]. Approximately 2600 *Salmonella* serovars were separated into two types: *Salmonella bongori* is less common and is associated with cold-blooded animals; while *Salmonella enterica* involves many serovars that infect both humans and animals [4]. *Salmonella* infections caused by *Salmonella* can vary from simple gastroenteritis to serious diseases such as typhoid fever or septicaemia. The primary modes of transmission are contaminated food or water, contact with infected animals, and poor sanitation [5]. *Salmonella* infections cause millions of foodborne illnesses every year, making it a serious global public health concern. According to the World Health Organization (WHO), *Salmonella* is among the top five organisms that cause foodborne illnesses worldwide [6]. The most prevalent illness is caused by non-typhoidal *Salmonella* (NTS) infection, usually presenting as gastroenteritis. Typhoid fever, however, is a more serious systemic disease caused by typhoidal *Salmonella* (e.g., *Salmonella typhi* and *Salmonella paratyphi*) infection, which can be lethal if not addressed properly [7].

The prevalence of *Salmonella*-related diseases is very high in low- and middle-income countries (LMICs) because access to clean water, sanitary facilities, and medical treatment is restricted in such regions. Epidemics in these areas are likely to increase morbidity and mortality, especially among vulnerable populations such as children, the elderly, and immunocompromised individuals [8]. Despite improvements in food safety methods and control techniques, *Salmonella* remains one of the leading causes of foodborne infections in high-income and low-income countries, especially poultry and eggs [9]. The antimicrobial resistance (AMR) of *Salmonella* has raised significant concerns worldwide as a public health issue. The number of multi-drug resistant (MDR) *Salmonella* strains is increasingly obscuring the treatment of infections and causing treatment failure [10]. Resistance of *Salmonella* can result from routes such as selection under antibiotic pressure, mutation, or horizontal gene transfer (HGT) gain of resistance genes [11]. The primary handler of the emergence of AMR has been the overuse and misuse of antibiotics in human medicine and agriculture [12]. In particular, the unsuitable use of antibiotics for the treatment of human foodborne infections and their use as growth accompaniments in cattle farming have contributed to creating an environment that would help select resistant *Salmonella* strains [13].

AMR among *Salmonella* presents several challenges: a higher rate of treatment failure, insufficient choices for alternative treatments, and unrelated impacts among susceptible groups [14]. Further outcomes associated with resistant strains include higher mortality rates, longer periods of infection, and higher medical expenses [15]. Moreover, a greater opportunity for acquiring other resistance occurs when subjected to antibiotics such as colistin and carbapenems [16]. Children, the elderly, and immunocompromised people are just some of the in-danger populations that are more exposed to unfavorable consequences [17]. AMR also carries huge financial implications in terms of the length of hospital stay, cost of diagnostic procedures, and cost of treatment plans [18]. Economic losses can also be seen in the food and agriculture sectors, mainly through trade restrictions on adulterated foods and customer loss of confidence in the safety of foods [19]. This review identifies new resistance trends, common mechanisms, and geographic trends, in addition to exploring some of the recent trends of AMR in *Salmonella* strains. It also explores how MDR strains spread and how they correspond to various foods and clinical diseases. The main contributors to AMR among *Salmonella* are antibiotics used in veterinary practice, human health, and agriculture, as well as environmental determinants, including soil and water contamination. Finally, we discuss the importance of genetic exchange between *Salmonella* strains and other bacteria [20]. The evaluation will investigate how AMR impacts food safety, where resistant strains make it harder to control foodborne illnesses, and have implications for treatment outcomes. In addition, wider implications for public health, especially for the disadvantaged, are reviewed. The assessment also discusses the means of countering AMR in *Salmonella* through improved food safety practices, alternative treatments, and enhanced antibiotic stewardship [21]. The report also discusses the role of surveillance systems, international cooperation, and national and international regulatory frameworks in resolving the AMR crisis. To grapple with the crisis on a holistic level, the review will lastly consider the potential of One Health initiative, which combines the realms of human, animal, and environmental health (Fig. 1).

2. Mechanisms of AMR development in *Salmonella*

Salmonella AMR makes infection control and treatment challenging, and the practice involves chromosomal gene mutations, horizontally acquired resistance genes, and mobile genetic elements [22]. However, these are usually conditioned by selective pressure from intensive antibiotic use in both human and veterinary medicine. Intrinsic resistance is the natural ability of *Salmonella* to resist certain antibiotics because of its inherent genetic characteristics [23]. Many *Salmonella* strains that acquire resistance genes from other bacteria can easily become MDR. In most cases, this is achieved through HGT. HGT is the primary mechanism by which resistance genes are acquired [24]. There are three main forms of HGT: conjugation, transformation, and transduction [24]. Bacteriophages are viruses that infect bacteria and transfer genetic material between two different bacteria via transduction [25]. During infection, phages transfer resistance genes from one bacterium to another. *Salmonella* produces enzymes known as extended-spectrum β-lactamases (ESBLs), which hydrolyze monobactams and extended-spectrum cephalosporins, rendering them ineffective [26]. Enzymes, referred to as carbapenemases, degrade carbapenems; thus, antibiotics are less effective at treating severe infections caused by resistant organisms [27]. Aminoglycoside resistance is a common characteristic of *Salmonella* species, and mutations in *tetA* and *tetB* genes confer resistance to tetracycline [28]. Mutations in *gyrA* and *parC* encode DNA gyrase and topoisomerase IV, respectively, which lead to the development of quinolone-resistant *Salmonella* [29]. Mobile genetic elements (MGEs) play a central role in the establishment and spread of antibiotic resistance in *Salmonella*, aiding the rapid spread of resistance features by transferring resistance genes among bacteria [30]. Knowing how AMR develops (Figs. 1 and 2) is important in formulating efficient plans to combat resistant strains and tackle AMR related disease (Table 1).

2.1. Resistance mechanisms against common antibiotics in Salmonella

Integrons are bacterial genetic structures that can select and express genes, particularly those associated with antibiotic resistance [31]. They can be imagined as molecular “toolboxes” that enable bacteria to rapidly adjust to antibiotics by incorporating new “tools” (genes) whenever necessary. These genes are usually carried in small packets, referred to as gene cassettes [32]. When integrated, these cassettes are expressed, enabling the bacteria to become resistant to many antibiotics. Integrons play a central role in the dissemination of multi-drug resistance, particularly when integrated with mobile DNA, such as plasmids or transposons [33]. Efflux pumps are protein-mediated transport systems present in the bacterial cell membrane. They are responsible for pumping toxic compounds such as antibiotics out of bacterial cells [34]. When an antibiotic penetrates a bacterial cell, the efflux pump recognizes it as a danger and actively ejects it before it can cause harm. This reduces the drug concentration inside the cell, making the antibiotic less effective [35]. Efflux pumps are a dominant mechanism of resistance, frequently causing multi-drug resistance because they can expel several classes of antibiotics simultaneously [36].

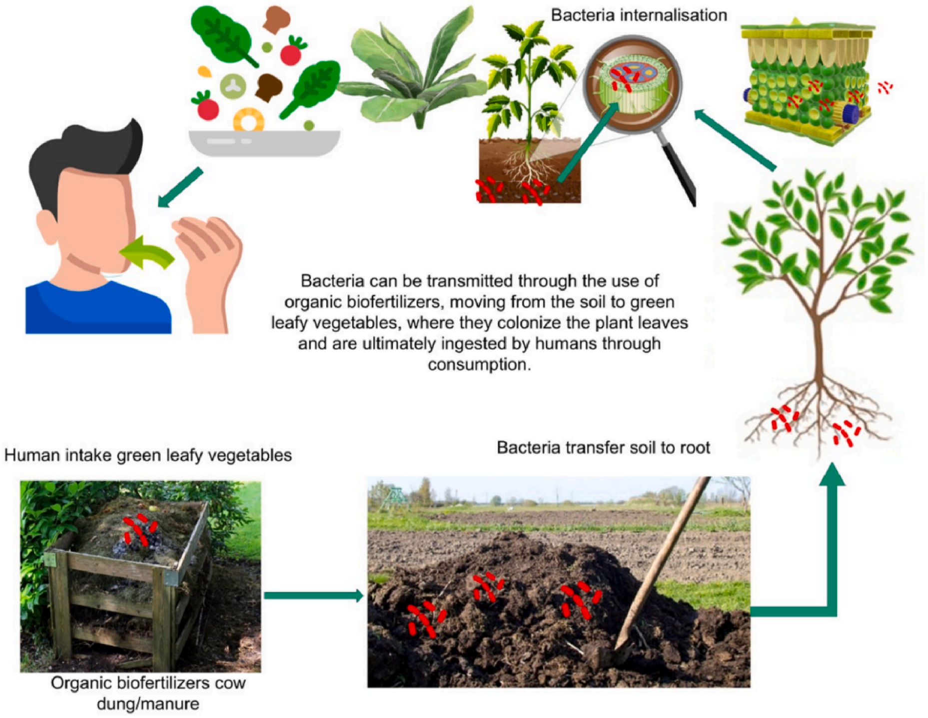

Fig. 1. Transmission of antimicrobial resistance pathogens from environmental sources to human.

With resistance mechanisms that continue to evolve to combat various antibiotics, AMR of *Salmonella* strains poses a serious problem concerning treatment [10]. Through these mechanisms, *Salmonella* can avoid the effects of common drugs such as tetracyclines, β-lactams, aminoglycosides, fluoroquinolones, and third- and fourth-line antibiotics [37]. The emergence of MDR strains and improved resistance in both typhoidal *Salmonella* and NTS highlight the need for the development of diagnostic, treatment, and defensive approaches [38]. β-lactam antibiotics such as penicillin and cephalosporins are among the most commonly-used drugs for treating bacterial infections, including *Salmonella* infections [39]. β-lactamase enzymes that break down the β-lactam ring and make the antibiotic inactive have emerged as a source of resistance [40]. Many β-lactamases, including AmpC and ESBLs, which break down the β-lactam ring and prevent the antibiotic from binding to its target, and penicillin-binding proteins (PBPs) are produced by *Salmonella* species [41].

Aminoglycosides such as gentamicin and amikacin are often used to treat serious infections caused by *Salmonella*. However, resistance to aminoglycosides among *Salmonella* is increasing, mainly due to mutations in antibiotics by specific enzymes [42]. The formation of aminoglycoside-modifying enzymes (AMEs) which alter the shape of the medication and prevent it from binding to its bacterial target, the 30S ribosomal subunit, is often responsible for AMR production [43]. Ciprofloxacin is a fluoroquinolone commonly used to treat *Salmonella* infections, including those caused by NTS and Enterobacteriaceae [38]. *Salmonella* resistance to fluoroquinolones is usually caused by mutations in genes encoding topoisomerase IV (*parC*) and DNA gyrase (*gyrA*), both of which are necessary for DNA replication [29]. Acquiring resistance genes from plasmids, which may contain resistance determinants encoding efflux pumps, is another way to bestow plasmid-mediated resistance [44]. For many years, tetracyclines such as doxycycline and tetracycline have been used to treat *Salmonella* infections. However, due to the development of ribosomal protection proteins and efflux mechanisms, *Salmonella* has become resistant to tetracycline [35] (Table 1).

2.2. *Resistance to third- and fourth-line antibiotics*

Salmonella has become resistant to third- and fourth-line antibiotics such as colistin and carbapenems, which are last-resort therapies, as resistance to first- and second-line antibiotics increases [53]. Although carbapenems are frequently used to treat infections that are resistant to several drugs, the advent of resistant *Salmonella* strains is causing increasing concern [54]. Generally, the mechanism of resistance to carbapenems involves the production of carbapenemases, including *Klebsiella pneumoniae* carbapenemases (KPC) and metallo-β-lactamase (MBL), which depreciate the carbapenem structure and make the antibiotic unusable [55]. Because of their ability to be transferred from patient to patient, it is common for carbapenem-resistant *Salmonella* bacteria to correlate with hospitals and healthcare environments [56]. This polymyxin antibiotic is frequently used as a last alternative in the treatment of infections caused by MDR gram-negative bacteria, including *Salmonella*. Normally, these bacteria have mutations in the *pmrA* and *pmrB* genes, which modify the bacterial cell membrane to reduce colistin binding [57,58]. The plasmid-mediated spread of colistin resistance is of specific importance in countries where colistin is extensively used in agriculture [59]. MDR *Salmonella*, which are resistant to numerous classes of antibiotics, are a serious public health concern. They are challenging to treat because they often anchor multiple resistance genes to plasmids or other mobile genetic elements [60]. MDR *Salmonella* strains are difficult to treat because of insufficient therapies. Most of the time, they are associated with foodborne illnesses.

3. Global trends and geographic variability of AMR in *Salmonella*

The WHO is implementing surveillance initiatives to monitor AMR in *Salmonella*, a global public health issue [61]. The Global Antimicrobial Resistance Surveillance System (GLASS) collects information from hospitals, laboratories, and governmental surveillance systems worldwide, forming the basis for evidence-based policies to control antibiotic

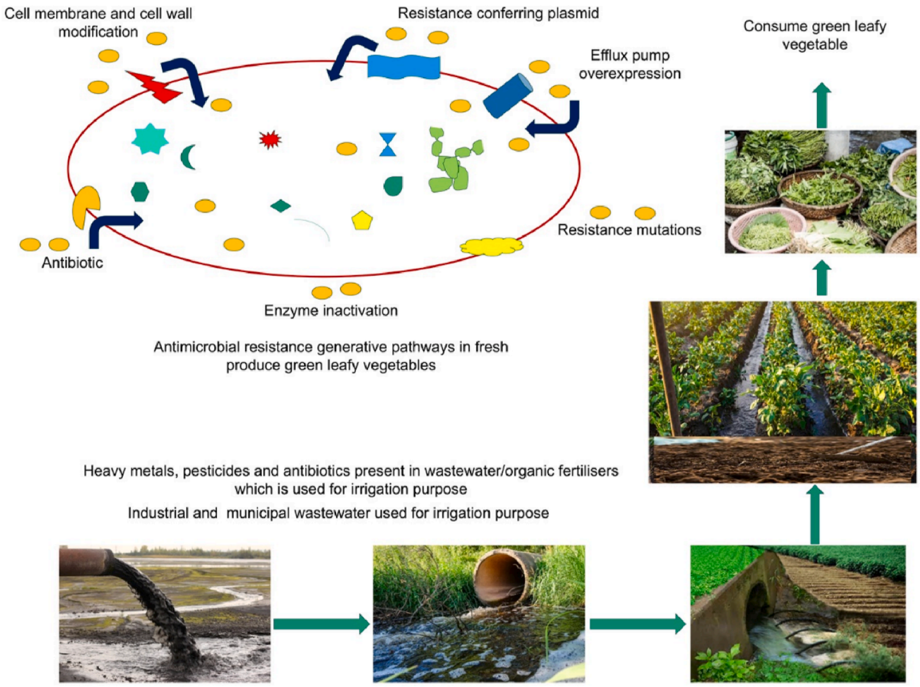

Fig. 2. Generation of antimicrobial resistance from environmental sources.

Table 1
Mechanisms of the development of AMR in *Salmonella*.

Mechanism	Types of resistance	Phenotypic traits	Genotypic traits	Reference
HGT	MDR	Resistance genes are acquired through integrons, transposons, or plasmids	*intl1, intl2* (class 1 and 2 integrons)	[45]
Colistin resistance	Polymyxin	LPS alterations decrease colistin binding	*mcr-1, mcr-2, mcr-3*	[46]
Permeability reduction	Carbapenem	Drug absorption is decreased when porin channels are lost	Mutations in *pmpC and ompF*	[47]
Ribosomal modification	Macrolide	Decreased ribosome binding of macrolides (such as azithromycin)	*ermA, ermB, mphA*	[48]
Plasmid-mediated resistance	Aminoglycoside	Aminoglycoside inactivation (gentamicin, kanamycin, etc.)	*aadA, aphA1, aac(3)-IV*	[49]
Target site alteration	Fluoroquinolone	Decreased susceptibility to fluoroquinolones (such as ciprofloxacin)	Mutations in *gyrA, parC, and parE*	[50]
Enzymatic inactivation	β-lactam	β-lactam antibiotics, such as cephalosporins, and penicillins, are hydrolyzed	*blaTEM, blaCTX-M, blaSHV, ampC*	[51]
Efflux pumps	MDR	Decreased vulnerability to some antibiotics (such as tetracyclines and quinolones)	*acrAB-tolC, emrAB, mdtK*	[52]

Abbreviations: AMR, antimicrobial resistance; HGT, horizontal gene transfer; MDR, multi-drug resistant; LPS, lipopolysaccharide.

resistance [62]. The relationship between the environment, economy, and antimicrobial peptides (AMPs) in these regions is discussed in detail (Supplementary Table 1). Some nations have established national monitoring systems, such as the European Antimicrobial Resistance Surveillance Network (EARS-Net) and U.S. National Antimicrobial Resistance Monitoring System (NARMS), to monitor the development of resistance in *Salmonella* isolates from humans, animals, and retail meat [63]. Overuse and abuse of antibiotics in agriculture and human health care have caused *Salmonella* infections, particularly MDR forms, which is a significant public health problem across Asia [64]. Lax regulations in agriculture, particularly in veterinary use, are a major factor contributing to AMR in Africa [65]. The European Union conducts surveillance on AMR in zoonotic and indicator bacteria from animals, humans, and food. The data collected is jointly analyzed by the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control. In the period of 2019–2020, *Salmonella* spp. isolated from human cases exhibited high resistance to ampicillin, sulfonamides, and tetracyclines, while demonstrating very low resistance (0.8 %) to third-generation cephalosporins, specifically cefotaxime and ceftazidime. Resistance to ciprofloxacin was moderate in human *Salmonella* isolates, with an exceptionally high resistance rate (82.0 % in 2020) observed in *Salmonella* serovar Kentucky, alongside increasing resistance trends in *Salmonella enterica* serovar Enteritidis across nine countries from 2016 to 2020 [66] (Table 2).

3.1. Geographical, food production, and healthcare system-based variations in resistance patterns

Salmonella AMR is more common in regions such as Asia, Europe, and North America, where intensive animal husbandry and extensive antibiotic usage in livestock production are prevalent [70]. The linkage between resistant strains and animal development causes this resistance, and contaminated food products spread these strains among people [71]. Conversely, less industrialized farming systems, such as those in certain regions of Africa, may not have a significant effect on AMR, but abuse and overuse in comparison to human health still have a lot of influence [72]. The healthcare infrastructure plays a significant role in the development and spread of AMR. Controlling prescriptions of

Table 2
Geographic and global variability of AMR (source of data: https://resistancemap.onehealthtrust.org/Countries.php) and resistance trends.

Area	Resistance trends	Drivers of resistance	Reference
Asia	High prevalence of third-generation cephalosporin, ciprofloxacin, and colistin-resistant MDR pathogens, especially in China and India	Antibiotic overuse and abuse in aquaculture and cattle, as well as uncontrolled over-the-counter sales	[67]
Oceania	Stricter antibiotic use regulations have resulted in lower overall resistance rates; yet there is occasionally resistance in imported food items	Strict laws and a heavy reliance on imported food could spread resistant strains	[68]
South America	There is widespread ampicillin and tetracycline resistance, and in certain areas, there is growing carbapenem resistance	The use of antibiotics in healthcare and agriculture is unregulated, and stewardship initiatives are not fully implemented	[67]
Africa	β-lactam and quinolone resistance are frequent in MDR pathogens, yet there is little information on AMR surveillance in many areas	Reliance on empirical treatment, inadequate access to tests, and weak regulatory frameworks	[68]
Europe	MDR *Salmonella* serotypes, particularly Typhimurium and Enteritidis, were found; resistance to earlier antibiotics (ampicillin, sulfonamides) was widespread	Although legacy resistance in animal and human isolates still exists, strict antibiotic regulations lessen resistance to important medications	[68]
North America	Resistance to ceftriaxone and fluoroquinolones is on the rise, while ampicillin, tetracyclines, and streptomycin is highly prevalent	Intensive farming methods, excessive use of antibiotics in animal feed, and enhanced surveillance to spot resistance patterns	[69]

Note: additional information for resistance trends can be found in Supplementary Table 2. Abbreviations: AMR, antimicrobial resistance; MDR, multi-drug resistant.

antibiotics and equipment for diagnostics help to control abuse in developed healthcare systems. Nonetheless, over-the-counter selling of antibiotics, inappropriate regulation of antibiotic use, and infection control procedures all play a role in the occurrence of resistant *Salmonella* types in LMICs that are poor, illiterate, and lack proper sanitation. Socioeconomic factors, including poverty, illiteracy, and low sanitation, influence AMR trends in *Salmonella* [73]. One of the major causes of AMR is the overuse of antibiotics in veterinary medicine, human health, and agriculture. In high-income countries, antibiotics are extensively prescribed to treat human and veterinary diseases, creating resistance factors. Abuse of antibiotics is more prevalent in LMICs, where they can be bought by anyone and sold without a prescription, which enhances the spread of resistant strains [74].

4. The impact of AMR in *Salmonella* on food safety and public health

The ever-present problem of AMR among *Salmonella* grows worse only with time; MDR forms of the bacterium are an increasing challenge and complicate the choice of treating infections. This issue affects not only human health but also societal and economic systems that rely largely on the safety of food products. Understanding the foodborne mechanisms of transmission, health implications, and economic ramifications of AMR in *Salmonella* is essential for the development of successful public health policies and interventions [6]. *Salmonella* is one of the leading causes of foodborne illnesses worldwide and contaminates many different types of food, most of which are animal-based, including fresh fruit, poultry, eggs, and dairy products [75]. *Salmonella* can be corrupted from farms to tables at any stage of the food-manufacturing process. *Salmonella* contamination is commonly associated with poultry products such as chickens and turkeys [76]. Since *Salmonella* lives in the ovaries of infected hens, it can be transmitted through eggs by entering the eggshell or egg contents. *Salmonella* can also spread through dairy products, particularly unpasteurized milk and cheese [77]. Contamination of fresh produce is now well known, and most outbreaks have been linked to contaminated fruits and vegetables that were mishandled at the level of manufacturing, shipping, or consumption [78].

4.1. Routes of transmission to humans

Humans are infected with *Salmonella* through contaminated food, water, or direct contact with infected animals or their environment [79]. Phage therapy, which uses bacteriophages to target and combat bacterial infections, presents a promising alternative treatment. From the perspective of phage-mammalian immune system interactions, Zou et al. [80] provide the first systematic overview of the factors influencing phage therapy, such as the mode of administration, the patient's physiological status, and the biological properties of the phage, offering valuable insights for improving its application in treating various human diseases. The most common form of *Salmonella* infection occurs through the ingestion of foods that are often due to inappropriate handling, undercooking, or cross-contaminated food preparation [81]. Exposure to infected animals, runoff from agricultural operations, or poor sanitation may also contaminate water. *Salmonella* epidemics can also be caused by direct contact with infected animals, particularly in agricultural settings, or by encountering animal excrement [82]. *Salmonella* infections have recently been reported to be increasingly difficult to manage because of AMR growth, thus increasing morbidity and mortality, particularly in susceptible groups [14]. Colistin, a last-line-of-defense antibiotic used to treat MDR Gram-negative infections, has increasingly lost its effectiveness due to the emergence of colistin resistance particularly in pathogens such as *Salmonella*, *Escherichia coli*, and *Klebsiella* spp. This growing resistance has serious implications for AMR-driven morbidity and mortality. Colistin resistance is a key driver of enhanced morbidity and mortality, especially among immunocompromised and at-risk populations [14]. Until recently, resistance to colistin was mainly caused by the *mcr*-type mobile colistin resistance genes (e.g., *mcr*-1 to *mcr*-10), usually harbored on plasmids. More recent evidence, however, points to the precursors encoded on the chromosome playing a significant role in the development of mobile elements, offering a broader view of pathways to resistance. Groundbreaking research made the new discovery of non-mobile colistin resistance (*nmcr*) genes, which for the first time discovered three new chromosomally encoded colistin resistance genes *nmcr*-3, *nmcr*-4, and *nmcr*-5 and explained their phylogenetic connection to recognized *mcr* genes [83] (Table 3).

Identification of *nmcr* genes and their recognized evolutionary relationship with mobile colistin resistance determinants redraws our conception of how resistance factors arise and transmit [83]. It offers a missing evolutionary bridge between chromosomal and mobile resistance, underlining the necessity of incorporating environmental genomics, clinical surveillance, and evolutionary biology into One Health AMR programs. Such observations corroborate and add strength to the interpretation of rising resistance-related morbidity and mortality, especially as mobile resistance remains to significantly outpace antimicrobial innovation. In addition to requiring longer stays in hospitals and a greater risk of consequences that may include sepsis, organ failure, or chronic diseases such as arthritis, MDR *Salmonella* strains tend to be more serious and difficult to treat in general [84]. Treatment failure due

Table 3

Characteristics of chromosomally encoded colistin resistance (*nmcr*) genes.

Chromosomal gene	Mobile counterpart	Host species (representative)	Mode of resistance	Implication
nmcr-3	*mcr*-3	*Aeromonas*	PEtN modification of LPS	High similarity supports ancestral link
nmcr-4	*mcr*-7	*Aeromonas*	LPS modification pathway	Evolutionary intermediate
nmcr-5	*mcr*-5	Betaproteobacteria	Lipid A remodelling	Source of mobile variants

Abbreviations: PEtN, phosphoethanolamine; LPS, lipopolysaccharide.

to AMR may increase mortality rates, especially among patients with severe infections or those who are not administered proper medications immediately [85]. Owing to the increasing resistance to first-line antibiotics, such as cephalosporins and fluoroquinolones, medical professionals are bound to select less expensive, more toxic, or less effective alternative medicines that entail more side effects and prolonged treatment periods [86].

4.2. Public health and socioeconomic consequences of AMR Salmonella

In addition, certain populations, such as children, elderly people, and those with impaired immune systems, can develop significant health issues due to *Salmonella* infection [87]. Even though elderly people are vulnerable to impaired immune systems or underlying medical conditions, children are more likely to be vulnerable to severe illness owing to their underdeveloped immune systems and lighter body weight [88]. Severe infections are more likely to occur in immunocompromised individuals, such as those with HIV/AIDS, cancer patients, or recipients of organ transplants [89].

Salmonella AMR has worrying economic consequences because it affects the food industry, healthcare systems, and the world economy [90]. Since AMR does not respond well to medical treatments, such as alternative antibiotics, costly intensive care therapies, added diagnostic testing, and longer periods in the hospital, more all-embracing medical resources are necessary in such cases [91]. As more complex treatments are needed and complications such as organ failure or sepsis may arise, hospitalization is usually at a much higher rate [92]. This burden is further impaired because alternative antibiotics and medications are often more expensive than regular drugs [93]. AMR can also create industry barriers between nations, especially where antibiotic resistance of foodborne pathogens is a public health issue. If certain nations ban imports from areas with high AMR rates, this could have an impact on global food trade. Lastly, the increasing prevalence of resistant strains in the food chain may undermine consumer trust in Food Safety, which would lower the sales of certain *Salmonella* related products. The dynamics of the market may have been significantly affected by this.

5. Drivers of AMR in *Salmonella*

AMR in *Salmonella* is a developmental issue that is affected by various environmental, social, animal, and human factors. The agricultural industry, particularly animal production, is the primary driver of AMR as it exposes bacteria to antibiotics for growth promotion and disease prevention [12]. Antibiotic abuse and overuse are caused by lax regulations and enforcement in agriculture, especially in LMICs which permit farmers to use antibiotics carelessly. Another factor in the emergence and dissemination of resistant strains is improper use of antibiotics in medical facilities [94]. MDR bacteria are difficult to treat because of the overuse of broad-spectrum antibiotics. In many places, particularly LMICs, self-medication and prescription access to antibiotics results in inappropriate selection and dosage, which permits resistant bacteria to proliferate and survive in the body [93]. Environmental contaminants, such as wastewater, manure, industrial waste, and hospital waste, are responsible for resistance [65]. Contaminated environments and water sources facilitate the transmission of resistance genes, with animals near infected sources acting as vectors, thereby impacting aquatic systems and wildlife [95]. Globalization of trade and travel has contributed to the rise of AMR in *Salmonella* owing to the easy dissemination of resistant strains beyond restrictions [96]. Food products contaminated with microorganisms that are delivered to countries with less strict food safety controls, and global traffic of meat, poultry, and dairy products increase the risk of importing and exporting resistant pathogens [97].

6. Strategies to combat AMR in *Salmonella*

Global AMR of *Salmonella* requires a multi-faceted approach that involves alternative medicines, improved surveillance systems, and antibiotic stewardship programs [98]. Agriculture should completely limit the use of non-therapeutic antibiotics in livestock and poultry, and the health sector should encourage prudent antibiotic use through antimicrobial stewardship programs [99]. In recent years, phages have gained significant attention as emerging biocontrol agents in food safety. Among these, the novel phages vB_SalS-LPSTLL [100], LPST94 [101], LPSEYT [102], LPSE1 [103], and LPEK22 [104] have shown considerable potential in combating *Salmonella* contamination in food products. Given the rising issue of AMR, phages offer a viable alternative to conventional antibiotics. These phages demonstrate distinct advantages, including a broad host range, high lytic activity, and robust resistance, positioning it as an effective chassis phage for food safety applications. Other similar effective chassis phages include LPCS28 [105], LPVP [102], and LPRS20 [106].

However, clinical applications of phages face significant challenges, particularly in maintaining their therapeutic efficacy during gastrointestinal transit. Factors like gastric acidity, digestive enzymes, and bile salts can degrade and denature phages, compromising their viability. Recent studies have systematically evaluated current phage encapsulation technologies (such as alginate microspheres, liposomes, and chitosan nanoparticles) and identified their limitations [107,108]. To address these challenges, a novel co-encapsulation strategy has been first proposed, combining phages with probiotic strains. This dual-component delivery system holds great promise for microbiota modulation, simultaneously targeting pathogenic bacteria and promoting gut microbiome homeostasis [109]. This new therapeutic model offers an innovative approach to combating pan-drug-resistant bacterial infections by: (1) enhancing phage protection during gastrointestinal transit, (2) improving phage colonization efficiency in the gut, and (3) enabling multi-tiered ecological regulation of the intestinal flora.

To this end, policies controlling their use in animal husbandry and promoting antibiotic-free practices should be implemented through regulation of essential antibiotics in food production [110]. While vaccinations and other therapies should be promoted to reduce bacterial load and diminish dependency on antibiotics, molecular diagnostics and genomics can be used to detect and monitor the spread of resistance genes among *Salmonella* strains [14]. Prominent sanitation policies, proper food management, storage, and administration, in combination with food safety certification programs, should be adopted to promote food safety and hygiene practices. Schemes for public alertness and instruction campaigns should be relaunched to make consumers aware of the importance of using antibiotics correctly and safe food preparation techniques [111]. An integrated approach, combining various biomedical strategies to address the global threat of AMR in *Salmonella*, is summarized in Fig. 3.

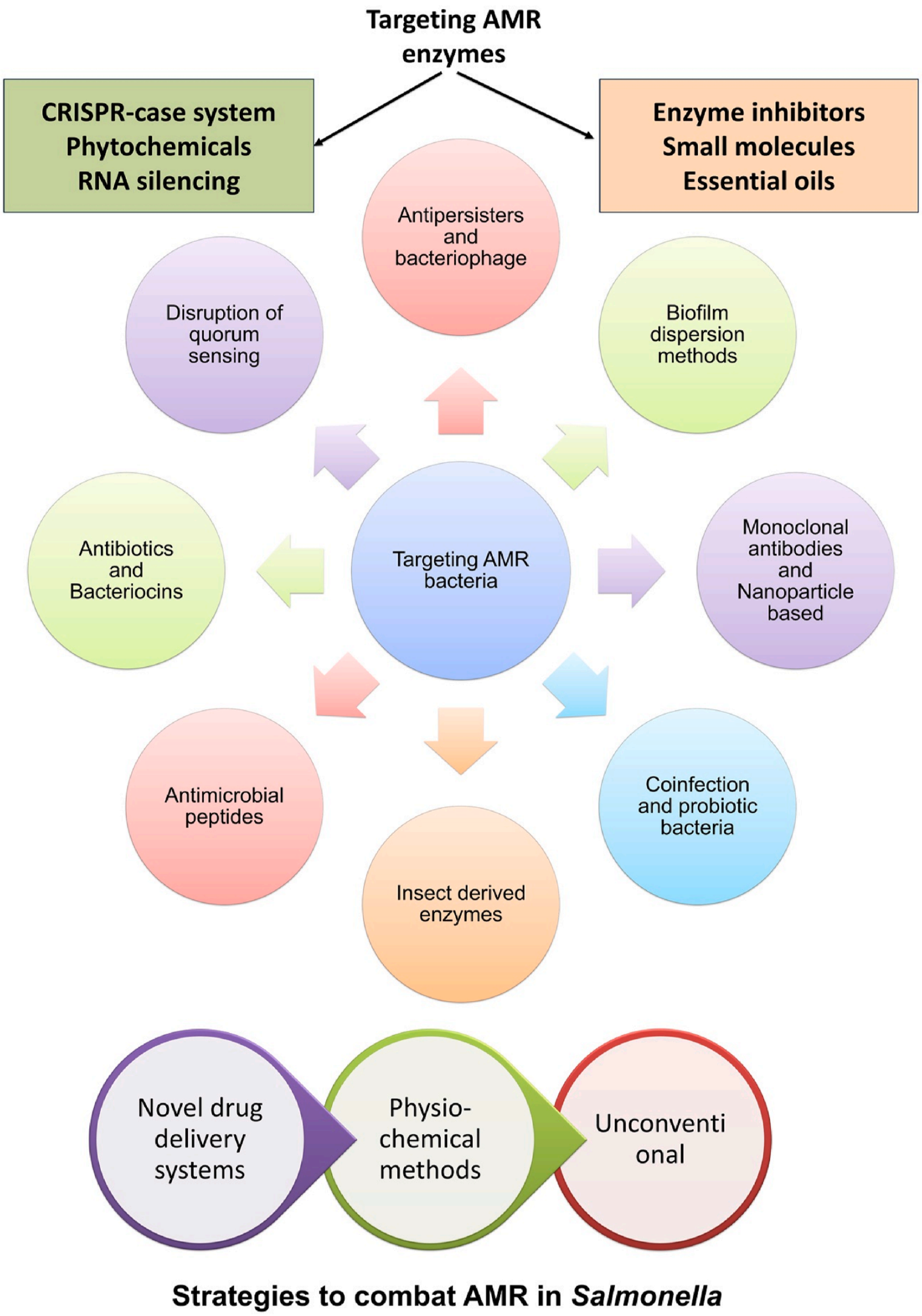

Fig. 3. Strategies to combat AMR in *Salmonella*. Abbreviation: AMR, antimicrobial resistance.

6.1. *One Health approach to address AMR in Salmonella*

The One Health approach to combat antibiotic resistance in *Salmonella* involves efforts across sectors and scales, with particular attention to the potential for AMR strains to contaminate water systems. Factors leading to the development of AMR include the use of antibiotics to enhance livestock growth, animal health, and the food supply chain. The cycle of resistance is sustained by AMR genes stored in environmental health, antibiotic residues, and resistant bacteria in sewage, untreated wastewater, and agricultural runoff [112]. Cross-sectoral collaboration is essential for effective reduction of AMR. Agriculture should ensure prudence in the use of antibiotics in agriculture, livestock, and aquaculture production, while the health sector should strengthen its infection prevention and control capabilities. Under national and regional AMR action plans, environmental sectors will enforce multi-sectoral coordination, monitor and reduce environmental reservoirs of AMR, and strictly impose regulations on waste and agricultural runoff treatment. While non-governmental organizations can increase awareness of AMR and safe food production and consumption practices in the community, the national action plan on AMR should be coordinated by governments with regional and international recommendations. The private sector should invest in the development of alternatives to antibiotics and the adoption of transparent and sustainable food production methods.

7. CRISPR technology in combatting AMR

CRISPR is short for “clustered regularly interspaced short palindromic repeats.” The development milestones of CRISPR technology (2022–2025) is summarized as follows.

Table 4
Suggestion for reducing AMR.

Aspect	Region of example	Observation	Reference
Healthcare systems	Low- and middle-income countries	Antibiotics sold over the counter and inadequate regulations lead to widespread *Salmonella* resistance; antibiotic stewardship initiatives and improved diagnostic tools prevent the overuse of antibiotics, which lower the overall number of resistant strains in low- and middle-income countries	[67]
Food production	European Union and Australia	When antibiotics are overused to promote growth, resistant bacteria develop, especially to the last-resort drug colistin; restrictions on the use of antibiotics have reduced the occurrence of AMR *Salmonella*, although environmental contamination is still a risk	[120]
Geography	Developed countries like the United States, European Union, and developed countries in Asia	As newer antibiotics are strictly regulated in food production, there is a high frequency of resistance to older antibiotics like ampicillin and tetracyclines	[120]

CRISPR's breakout year (2024): The FDA approved CASGEVY®, a CRISPR-Cas9 gene-editing drug for treating sickle cell disease. The treatment entails editing blood stem cells to decrease the activity of a gene that causes the disorder [113].

Broadening CRISPR applications: Scientists are working on *in vivo* CRISPR therapies, which introduce gene-editing tools directly into the body, possibly simplifying treatment procedures [114].

Precision medicine revolution: CRISPR-Cas technology is progressing beyond DNA editing to epigenome manipulation, becoming a valuable tool for biomedical research (Supplementary Table 3) [115].

Next-generation β-lactamase inhibitors: New inhibitors xeruborbactam, taniborbactam, and durlobactam have demonstrated better biochemical performance against OXA-48-producing Enterobacterales, the principal driver of AMR [116].

Promising combination drugs: These include cefepime/zidebactam, meropenem/nacubactam, and sulbactam/durlobactam, which are turning out to be extremely effective against resistant strains of bacteria [117].

Clinical trials and safety: Evidence from studies on meropenem–vaborbactam (MEV) and imipenem–cilastatin/relebactam (ICR) shows enhanced survival rates and clinical efficacy in the treatment of complicated infections [118].

8. Challenges and future directions

AMR studies of *Salmonella* are challenging. Little is known about the molecular mechanisms underlying AMR. It is still not clear how *Salmonella* acquires and spreads its resistance genes. The roles of environmental reservoirs in sustaining and dispersing AMR remains obscure. Faster, more accurate, and more affordable diagnostic technologies are needed, especially molecular diagnostic methods, such as portable sequencing equipment and CRISPR-based techniques [119]. Alternative treatments and new antibiotics under investigation include phage therapy, probiotics, immunotherapies, and vaccinations. Other policy and regulatory challenges include the lack of a single international framework to guide the use of antibiotics and non-uniform national recommendations. In addition, regulatory gaps exist in LMICs. Future directions include multi-disciplinary research, strengthening of surveillance systems, advancement of artificial intelligence-driven models of prediction, and advancement of genomics and nanotechnology-based strategies. Hygiene regulation involving the use of antibiotics in the health and agricultural sectors also calls for international collaboration and policy changes. Organized education campaigns will have to target the public to adhere to hygiene guidelines and use antibiotics responsibly. These moves will help address the current problems and provide a more effective course of action for fighting *Salmonella* AMR. Suggestions to decrease AMR are summarized in Table 4.

Expanding on the artificial intelligence-driven strategies mentioned earlier, recent advances in phage-based technologies demonstrate two innovative pathways for combating antibiotic resistance. The first approach employs the “PhageAMP” prediction model, which combines convolutional neural networks and long short-term memory networks to achieve enhanced detection of short-chain phage peptides (<30 amino acids), demonstrating superior performance (F1-score = 0.89). This advanced model extends beyond conventional physicochemical analyses by incorporating innovative integration with the ESKtides (a database that provides a comprehensive library of antimicrobial peptides derived from phage peptidoglycan hydrolases, targeting ESKAPE bacteria, known for their multi-drug resistance) [121], enabling comprehensive assessment of AMPs' potential resistance risks. The system's unique capability to predict resistance development while characterizing AMP properties represents a significant advancement in computational antimicrobial discovery. Another solution is through lysins. Traditional lysin screening methods are inefficient and can only cover less than 1 % of lysins. One study developed a software called DeepLysin [122], which used artificial intelligence to discover new lysins from the “dark matter” of phages, and artificial intelligence model for large-molecule antibacterial proteins was proposed for the first time. Among 466 non-redundant lysin candidates, the activity of LLysSA9 was superior to that of the existing phase III clinical lysin CF-301, and it showed significant efficacy in animal models and skin infections.

9. Conclusion

The growing threat of AMR posed by *Salmonella* is a serious issue for environmental sustainability, public health, and food safety. Thus, it is self-evident how deeply interrelated this situation remains by emphasizing that resistant strains continue to exist in humans, animals, and the environment. Critical antibiotic resistance increases the complexity of treatment and raises morbidity, mortality, and medical expenses. Although little is known about the contribution of agricultural practices and environmental reservoirs to resistance, this information is crucial for effective intervention. Only with strong surveillance systems, alternate treatments, and leading diagnostic techniques can we slow down AMR progression. Action requires a multi-disciplinary, One Health approach that integrates efforts from all fields of agriculture, environmental protection, animal health, and human health. This approach increases public awareness of safe food production and handling methods, boosts surveillance, and encourages prudent use of antibiotics. Governments and other stakeholders should continue working together to combat AMR in *Salmonella*, protect public health, preserve the world's food supply, and secure a sustainable future for future generations.

CRediT authorship contribution statement

Rahul Kumar: Writing – original draft, Validation, Data curation, Writing – review & editing, Visualization, Project administration, Conceptualization. **Nurudeen Olatunbosun Adeyemi:** Data curation, Writing – review & editing. **Sourav Chattaraj:** Writing – review & editing, Writing – original draft, Data curation. **Wiem Alloun:** Writing – review & editing. **A.K.A.N.W.M.R.K. Thamarsha:** Data curation, Writing – review & editing. **Snežana Anđelković:** Writing – review &

editing, Data curation. **Debasis Mitra:** Writing – review & editing, Writing – original draft, Project administration, Data curation, Conceptualization. **Pankaj Gautam:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Conceptualization.

Ethical compliance

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.soh.2025.100117.

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