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Review Article

Pathogenicity, Epidemiology, and Advances in the Treatment of Multidrug-Resistant *Salmonella* Infections: A Narrative Review

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Abstract: *Salmonella* is a bacterial pathogen with significant morbidity and mortality in humans driven by environmental and socioeconomic factors. As the third leading cause of death in humans among diarrheal diseases, *Salmonella* is a major public health threat which demands integrated interventions. The pathogenicity, determinants, prevention, control, and treatment of MDR *Salmonella* infections were reviewed following a literature search on PubMed and Google Scholar which yielded 405 articles, of which 79 articles were selected after screening. Enteric fevers caused by typhoidal *Salmonella* serotypes - *S.* Typhi, *S.* Paratyphi A, *S.* Paratyphi B, and *S.* Paratyphi C are found only in humans in mostly developing countries, while food poisoning and gastroenteritis caused by NTS serotypes - *S.* Typhimurium and *S.* Enteritidis respectively found in humans and animals in developing and developed countries accounts for 70% of *Salmonella* infections in humans associated with eating contaminated food products of poultry origin and also causes iNTS disease in humans. Preventing *Salmonella* contamination of animal products, water, vegetables and fruits, and promoting the safety and quality of foods for human and animal consumption is achievable through food and water hygiene, personal and environmental hygiene, biosecurity, preservation of animal feeds, food safety and HACCP principles, and epidemiological surveillance. *Salmonella* infection is basically treated using antibiotics, however, the rise in MDR strains has resulted in treatment with antibiotic-alternatives including probiotics, prebiotics, and vaccines. Further research is recommended in treating iNTS disease, developing human vaccine against NTS, and using bacteriophages, antimicrobial peptides, organic acids, and essential oils as antibiotic-alternatives.

Keywords: Antibiotic-alternatives, Antibiotic-resistant, Multidrug-resistant, Prebiotics, Probiotics, *Salmonella* infection.

INTRODUCTION

Foodborne diseases are major public health problem worldwide especially in developing countries due to difficulties in attaining standard hygienic food handling practices and poor sanitation. These diseases are caused by different pathogens e.g. bacteria, viruses, fungi, and parasites. Among the foodborne pathogens, *Salmonella* species are of particular concern as causes of enteric fever, food poisoning, and gastroenteritis [1]. *Salmonella* infection is the leading bacterial cause of acute gastrointestinal illnesses worldwide and the third leading cause of death in humans among diarrheal diseases [2]. The risk of exposure to *Salmonella* infection is often driven by environmental and socioeconomic factors [3]. *Salmonella* is the major cause of bacterial enteric illnesses in both humans and animals. Raw and undercooked meat, poultry, eggs, milk, unwashed or poorly washed fruits and vegetables, and other foods and water which have been contaminated with fecal material of a host are common agents of *Salmonella* infection in humans [4]. Close contact with infected animals such as poultry, livestock, pets, and rodents also pose risks of infection [5,6]. However, most infections are due to ingestion of food contaminated by animal or human feces, such as by a food handler at a commercial eatery. *Salmonella* is a group of enterobacteria that causes foodborne illnesses such as typhoid and paratyphoid fevers in humans and salmonellosis in both humans and animals [7]. *Salmonella* infection can be either typhoidal or non-typhoidal. Common signs and symptoms of *Salmonella* infection include diarrhea, stomach (abdominal) cramps, fever, nausea, vomiting, chills, headache, and bloody stool [8]. Occasionally, more significant *Salmonella* infection can result in dehydration and other complications including reactive arthritis, and irritable bowel syndrome [9]. The old, young, and others with weak immune system are more likely to develop salmonellosis. Other risk factors include bottle feeding, frequent use of antacids or proton pump inhibitors, and conditions that impair the reticuloendothelial system function such as leukemia and lymphoma [6].

Generally, salmonellosis is simply an infection with *Salmonella*. It is a symptomatic infection caused by bacteria of the *Salmonella* genus. *Salmonella* is a genus of rod-shaped (bacillus) Gram-negative, anaerobic, facultative, non-spore forming bacterium of the family *Enterobacteriaceae* measuring between 2-5 microns long by 0.5-1.5 microns wide [10]. The genus *Salmonella* consist of two species namely *Salmonella enterica* (6 subspecies) and *Salmonella bongori* (no subspecies) [11]. The Kauffmann-White typing system classifies *Salmonella enterica* into 6 subspecies namely: *S. enterica* subsp. *enterica* (I), *S. enterica* subsp. *salamae* (II), *S. enterica* subsp. *arizonae* (IIIa), *S. enterica* subsp. *diarizonae* (IIIb), *S. enterica* subsp. *houtenae* (IV), and *S. enterica* subsp. *indica* (VI) [12]. As of 2010, 22 antigenically distinct serotypes (serovars) of *Salmonella bongori* have been identified, along with 2,659 different serotypes of *Salmonella enterica*, of which 1,586 serotypes belong to *S. enterica* subsp. *enterica* (I) [13]. Each serotype is differentiated by taxonomic group according to the Kauffmann-White classification on the basis of their somatic O (lipopolysaccharide) and flagella H antigens [14]. *S. enterica* subsp. *enterica* (I) serotypes include *S. enterica* serovar Typhi, *S. enterica* serovar Paratyphi A, B, and C, *S. enterica* serovar Typhimurium, *S. enterica* serovar Enteritidis, *S. enterica* serovar Dublin, etc. and is responsible for nearly 100% of *Salmonella* infections in mammals [15]. *S. enterica* subsp. *enterica* (I) can be found worldwide in humans and warm-blooded animals and is the only subspecies that cause disseminated human diseases. *S. bongori* and other *S. enterica* subspecies have mostly been isolated from cold-blooded animals, particularly reptiles and amphibians and rarely infect humans [14]. *S. enterica* subsp. *enterica* (I) subspecies is divided into two main groups: typhoidal and non-typhoidal. Typhoidal serotypes are adapted to and cause diseases in humans only, while non-typhoidal serotypes infect a range of animals, can be transmitted from animals to humans (i.e. zoonotic) and from humans to humans [16]. Typhoidal serotypes - *S.* Typhi and *S.* Paratyphi associated with typhoid fever and paratyphoid fever respectively are found only in humans, while the non-typhoidal serotypes, especially *S.* Enteritidis and *S.* Typhimurium associated with most cases of salmonellosis in mammals are broad host (ubiquitous) [14]. Typhoidal *Salmonella* (TS) is responsible for enteric diseases such as typhoid fever caused by *S.* Typhi and paratyphoid fever caused by either of *S.* Paratyphi A, *S.* Paratyphi B, and *S.* Paratyphi C. Paratyphoid is similar to typhoid characterized by diarrhea, fever, abdominal cramps, and vomiting [9]. In contrast, non-typhoidal *Salmonella* (NTS) is chiefly pathogenic in animals that constitute the host and reservoir for human infection such as poultry, pigs, goats, cattle, rodents, pets, etc. [16]. NTS consist of all other *S. enterica* subsp. *enterica* (I) serotypes including *S.* Typhimurium and *S.* Enteritidis which causes food poisoning and gastroenteritis respectively in both humans and animals [4,17]. *S.* Typhimurium causes clinical typhoid-like syndromes in infants but in adults they produce foodborne toxic syndromes (food poisoning), while *S.* Enteritidis causes inflammation of the stomach and intestines (gastroenteritis) in both young and old people [6].

To identify knowledge and research gaps, we carried out a narrative review of studies on the pathogenicity, environmental and socioeconomic determinants, prevention, control, and antibiotics treatment of *Salmonella* infections alongside advances in antibiotic-alternatives against multidrug-resistant (MDR) *Salmonella* infections in humans and animals.

METHODS

A narrative review of studies on *Salmonella* infection gathered through extensive academic literature search of online databases was conducted in April 2025. We searched PubMed and Google Scholar for original research articles, literature reviews, systematic reviews, and meta-analyses on *Salmonella* infection published in peer-reviewed English language journals between January 1, 2015 and March 31, 2025 to obtain wide-ranging information about the pathogen. The keywords included in the search are "*Salmonella* infection," "pathogenicity of *Salmonella* infection," "pathogenesis of *Salmonella* infection," "environmental and socioeconomic determinants of *Salmonella* infection," "prevention and control of *Salmonella* infection," "treatment of *Salmonella* infection," "antibiotic alternative treatment of *Salmonella* infection," "advances in treatment of *Salmonella* infection," Manual searches of other relevant articles and reference lists of primary articles found from initial searches were also conducted. Studies on pathogenicity, environmental and socioeconomic determinants, prevention, control, and treatment of *Salmonella* infection, as well as advances in antibiotic alternative treatment for *Salmonella* infection published from January 2015 were included in this review. We also included studies related to *Salmonella* infection in low- and middle-income countries (LMICs). Conference papers, editorials/opinion pieces, non-peer-reviewed articles, and gray literature were excluded. Non-English language publications and studies not related to pathogenicity, environmental and socioeconomic determinants, prevention, control, and treatment of *Salmonella* infection were also excluded from this review.

Both initial searches of the online databases and the manual searches of other relevant articles and reference lists of primary articles yielded a total of 405 articles. Following the screening of titles and abstracts and the full-text assessment of the articles meeting the inclusion criteria to assess their relevance to the review objectives, 79 peer-reviewed journal articles with detailed information on the pathogenicity, environmental and socioeconomic determinants, prevention and control, and advances in treatment of *Salmonella* infection were selected for inclusion in this narrative review [18-96]. The flow diagram of the selection of articles for inclusion in this narrative review is shown in Figure 1.

The narrative review involved a combination of thematic analysis and narrative synthesis. Relevant information obtained from the selected journal articles were synthesized according to sub-headings (themes) in line with the study objectives.

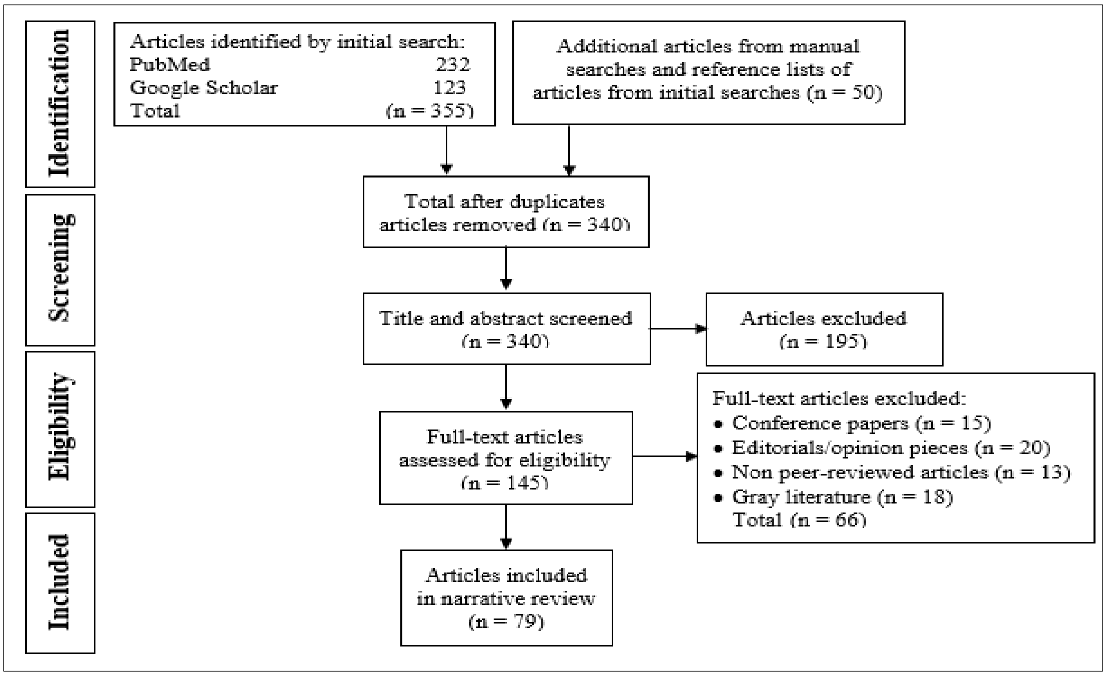

Figure 1: Flow diagram of the selection of articles for inclusion in narrative review

RESULTS

The narrative review synthesized all relevant information retrieved from the 79 selected journal articles on *Salmonella* infection and were presented in the following comprehensive sub-headings and paragraphs pertinent to the study objectives.

Pathogenicity

Salmonella infection is mostly via the fecal-oral route, through the ingestion of contaminated foods or drinks, or by direct contact with objects or animals in which the microorganisms are present. During ingestion, *Salmonella* enters the host's gastrointestinal tract and translocates into deeper tissues through a mechanism of rearrangement of the cell membranes of the enterocytes which forms part of the internalization process. Most *Salmonella* species possess peritrichous flagella which make them motile [18]. The ability of *Salmonella* to colonize its hosts through invading, attaching and bypassing the host's intestinal defense mechanisms such as the gastric acid is due to its flagella, capsule, plasmids, adhesion systems, and type III secretion systems [18]. *Salmonella* infection begins when the bacteria cross the epithelial surface of the small intestine, the primary site of infection and interacts preferentially with the Peyer's patches and the extension of infection occurs when *Salmonella* survive and replicate in the macrophages which is a privileged environment for evading the adaptive immune response [19]. Also, *Salmonella* interference with the activity of dendritic cells prevents its recognition by the host's adaptive immunity [20]. Several risk factors such as the dose of ingested microorganisms predispose the host to *Salmonella* infection. The number of bacteria that must be introduced for a healthy human host to develop a symptomatic *Salmonella* infection varies from 10^6 to 10^8 *Salmonella* per gram of food or water, however, in immunocompromised infants and children, the disease can be caused by the ingestion of as low as 10 CFU/ml of bacteria [19,21]. Other risk factors include gastric hypochlorhydria with a reduction in the first defensive barrier of the stomach, a condition of reduced gastric acidity resulting from rapid emptying of the stomach which is characteristic of infants, and decrease in humoral and cellular immunity, a characteristic of older people and immunocompromised individuals [22]. The incubation period of TS is 7-14 days, while NTS is 6-12 hours [20].

Infection with NTS is generally non-invasive and often results in food poisoning. The local response to the endotoxins is enteritis and gastrointestinal disorder [19]. In developed countries, NTS infection is mostly present as gastrointestinal disease which is usually uncomplicated and self-limiting and is rarely associated with systemic diseases, except in immunocompromised individuals who are at risk of severe complications such as bacteraemia, meningitis, and osteomyelitis among others, however, in some cases, particularly in sub-Saharan Africa, they can cause invasive NTS (iNTS) and create a major problem in bloodstream infections [19,23]. iNTS is mostly caused by *S.* Typhimurium or *S.* Enteritidis and is common among immunocompromised individuals, including those with certain primary immunodeficiencies (such as Mendelian Susceptibility to Mycobacterial Disease, Chronic Granulomatous Disease, and Sickle Cell Disease), as well as HIV/AIDS, malaria, and malnutrition in children and older age groups [24-26].

Environmental and Socioeconomic Determinants

Salmonella grow optimally at temperature of 5°C-37°C and most strains can survive a pH of 4-9 [27,28]. Compared to other Gram-negative bacteria, salmonellae are resistant to various environmental conditions including drying, salting, smoking, and freezing for varying lengths of time thus, can survive in many foods and frozen water. It can survive for days in ground water, pond, or seawater and for months in contaminated eggs and frozen oysters but die when exposed to temperatures of above 70°C for 15 minutes [29]. *Salmonella* lead predominantly host-associated lifestyles, but can persist in a lavatory setting for weeks following contamination, and are frequently associated with water sources which act as reservoirs and may help to facilitate transmission between hosts [30]. It is known for its ability to survive desiccation and can persist for years in dry environments and foods [30]. Salmonellae thrive in unclean water, soil, domestic and agricultural wastes, livestock, domestic and wild animals, and free-living wild birds [31]. In water contaminated with animal feces, salmonellae survive and multiply rapidly due to the nutrient level, however, in clean water the survival rate is lower [32,33].

Numerous studies identify low socioeconomic status to be correlated with increased incidence of enteric diseases such as *Salmonella* infection [19,34-36]. Socioeconomic factors including poverty, low education, unemployment, high cost of living, overcrowding, and social exclusion are associated with environmental factors such as poor sanitation and hygiene, inadequate waste and sewage disposal, and lack of access to potable water which can result in *Salmonella* infection in the form of enteric fever, gastroenteritis, or food poisoning [18]. *Salmonella* infections such as enteric fevers (typhoid and paratyphoid) which can be linked to poor sanitation and environmental hygiene have largely been eliminated in many parts of the developed world through improved sanitation, but continue to be a significant public health problem in developing countries. Enteric fever has become a barometer for gauging the environmental sanitation condition of a region or country as the incidence decreases when there is increase in controlled sewage system, proper waste disposal, pasteurisation of milk and dairy products, etc., however, where these hygienic conditions are lacking, the probability of fecal contamination of food and water remains high and so is the incidence of enteric fever [33, 37].

Prevention and Control

The prevention and control of *Salmonella* infection in humans and animals involves eliminating *Salmonella* contamination of animal products, water, fruits and vegetables, and enhancing food safety and quality. These can be achieved through a combination of the following measures:

Food and Water Hygiene

Water treatment by chlorination and filtration can interrupt the spread of *Salmonella* [38]. Boiling of tap water for about five minutes before drinking or brushing teeth with it, avoiding ice in beverages, eating well-cooked food that is steaming hot, vigorously washing fresh fruits and vegetables in hot water before eating, and thoroughly reheating food stored in freezers and refrigerators before eating are recommended [39]. Other hygiene measures include cooking poultry, beef, pork, and eggs thoroughly to destroy the bacteria before eating, avoiding food or drink containing raw eggs or raw (unpasteurized) milk and street-vended foods, regular washing of hands with soap and clean water while preparing food as well as before and after eating, and keeping kitchen utensils clean and dry after use [40].

Personal and Environmental Hygiene

Personal and environmental hygiene can be achieved by promoting WASH measures such as washing hands with soap and clean water after using the toilet; washing hands thoroughly and cleaning work surfaces immediately after changing diaper and after handling livestock, poultry, reptiles, and pets; avoiding direct and indirect contact between these animals and those with health problems; adopting waste disposal methods of landfilling and incineration to reduce wastes littering thereby ensuring a clean and healthy environment; and the use of water closet toilet system to improve sewage disposal and avoid open defecation [41,42].

Biosecurity

Biosecurity is crucial in minimizing the risk of environmental exposure to *Salmonella* contamination in animal houses [43]. Preventing *Salmonella* exposure among low-moisture and fermented feeds of animal origin can be achieved by having *Salmonella*-free animals including cattle, pig, poultry, fish, etc. The prevention of *Salmonella* infections in animals involves multiple interventions due to the ability of *Salmonella* to survive environmental changes associated with wide ranges of temperature and pH. The strategies for minimizing *Salmonella* exposure in the animal house include regular cleaning and disinfection to prevent contamination of successive groups of animals [44]. At slaughterhouses, it is important to have a minimum time animals are allowed to stay in pens to reduce cross-infections and cross-contamination [45]. During slaughtering, hide removal should be done appropriately to prevent the outside of the animal's skin from coming into contact with the flesh, and in meat processing, the processing unit and storage units should be separated and disinfection carried out routinely and supplemented with subjecting the meat to microbiological tests [46].

In poultry farms, *Salmonella* infections highly occur through dirty feet, feathers, feedstuffs, and water. To maintain the food safety of poultry products, including meat and eggs, *Salmonella*-free breed of birds should be introduced in the house. This can be achieved by screening and vaccinating each batch of flocks [47]. The *Salmonella*-free flocks should be raised by using hygienic feeds, having rodents, reptiles, and bird-proof housing, and farm workers wearing clean protective clothing [48]. Other biosecurity measures include disinfection of footwear and vehicles entering the poultry farm, cleaning water troughs, regular removal of droppings and litter, testing, culling and proper disposal of dead flocks and isolation of sick ones, and decontamination using strong disinfectant to maintain a safe environment for each batch of flocks in the poultry farm [45,49].

Biosecurity measures for fruits and vegetables include the treatment of farmyard manure to devitalize foodborne pathogens such as *Salmonella* before use in cultivation and irrigating fruits and vegetables with clean water as pathogens including *Salmonella* from contaminated water can enter plants through the stem system and stomata pore on the leaves [50]. Factory workers should also adhere to hygienic principles in fruits and vegetables processing [51].

Preservation of Animal Feeds

The presence of *Salmonella* in animal feeds such as grains, oilseed meals, and fish meals have been reported as a vehicle for the transmission of *Salmonella* in poultry and livestock [52]. Avoiding *Salmonella* contamination of animal feeds is important for the food safety of animal products and maintenance of human health by preventing transmission [53]. The preservation of animal feeds from *Salmonella* contamination can be achieved by heat treatment, use of organic acids, and other chemical preservatives [54]. Heat treatment of animal feeds at 80-85°C for about 5-12 minutes is considered sufficient to destroy *Salmonella* [29]. However, in some conditions, heat treatment at 80°C may not be sufficient for the destruction of certain *Salmonella* serotypes, hence, additional chemical compounds such as organic acids can be applied to animal feeds to reduce the pH value to below 4 thereby creating unfavorable conditions for the growth and survival of *Salmonella* [46]. Studies have shown that organic acids such as acetic acids and lactic acids inhibit the growth of *Salmonella* [55].

Food Safety and HACCP Principles

Hazard Analysis Critical Control Point (HACCP) is the logical system of food control based on prevention of contamination [46]. HACCP is superior to quality control and is the voluntarily acquired knowledge and skills of food processing companies about food safety management [46]. *Salmonella* infection can be prevented and controlled by implementing HACCP [56]. It ensures safe food supply to consumers through standards that deal with food safety management and are reviewed every 5 years to assess whether a revision is necessary to ensure that they remain relevant and useful to businesses. ISO 22000 is an international standard that specifies food safety management systems using HACCP principles to provide safe food products free from contaminants. Various countries have different agencies and parastatals that oversee the application of HACCP to avoid food safety disasters and governments impose the frameworks within which food safety issues can be managed which may include education and training on the causes and management of foodborne diseases and the standards of safe foods for humans [46,57]. Routine trainings are conducted for food industry practitioners, regulatory personnel, and supporting systems. The success of HACCP in several countries has led to calls to effectively use this management system to ensure food safety along the entire food chain from farm to table [41].

Epidemiological Surveillance

Many developed countries have established national and regional surveillance systems on Salmonellosis to create awareness, detect, and respond rapidly to outbreaks and halt the spread. The global consensus is to move towards whole-genome sequencing (WGS) for routine surveillance and outbreak detection for *Salmonella*, however, in the West African region including Nigeria, for instance, there is a lack of adequate population-based studies of *Salmonella* incidence or surveillance systems that can measure the rate of the disease at the population level [58]. Surveillance and collaboration across human health, food safety, and animal health experts and the combined efforts of the food industries, regulators, and public health officials are essential for controlling *Salmonella* along the food chains [59]. The global epidemiological surveillance of *Salmonella enterica* serotypes in animal-based products (beef, pork, poultry, and seafood) from 5 continents - Africa, America (North and Latin America), Asia, Europe, and Oceania found *S.* Typhimurium from all assessed products and continents with poultry playing a primary role in the transmission of *S.* Enteritidis in humans, whereas *S.* Anatum and *S.* Weltevreden serotypes were frequently reported in beef and seafood respectively [60]. Surveillance data are important in facilitating the identification of potential reservoirs for interventions. Considering the identified serotypes infecting humans, control programmes and specific interventions can be implemented to reduce the risk of salmonellosis in humans. Furthermore, reported outbreaks provide critical information on how to control the spread of the disease and prevent similar events in the future. Moreover, epidemiological surveillance provides sources of infections that support specific contamination and the need to monitor the effectiveness of the control measures which becomes critical components for all national public health and veterinary stakeholders to respond against human salmonellosis [46].

Treatment with Antibiotics and the Rise of Antibiotic-Resistant, Antimicrobial Resistant (AMR), and Multidrug-Resistant (MDR) Serotypes

In developed countries, NTS infection is usually associated with mild gastrointestinal illness which is self-limiting and antimicrobial treatment is not recommended [61]. Individuals at risk of complications with meningitis and septicemia may require treatment with antibiotic drugs, including ciprofloxacin, ceftriaxone, and ampicillin [62]. On the contrary, in sub-Saharan Africa, NTS infection can be invasive such as the reported incidence of iNTS disease in Malawi [63], thus, necessitates treatment with antibiotics alongside other antimicrobial drugs. TS infection by *S.* Typhi and *S.* Paratyphi can cause serious complications and require treatment with antibiotics such as cefixime, chloramphenicol, amoxicillin, trimethoprim/sulfamethoxazole (TMP-SMX), azithromycin, aztreonam, cefotaxime or ceftriaxone [64].

Over the years, the resistance of specific *Salmonella* serotypes to first-line antibiotics, as well as to other alternative drugs has emerged [65]. The rise of MDR *Salmonella* serotypes is due to a many factors, including excessive use of antibiotic drugs as a result of easy access (over the counter and internet sales) in some countries [62], the use of antibiotics for growth promotion in animal husbandry and for the protection of crops, and poor hygiene practices which contribute to the overuse of antibiotics inducing resistance [66,67]. The emergence of MDR strains that are resistant to first-line antibiotics became known in the 1980s, followed by *S.* Typhi reduced resistance to ciprofloxacin, quinolones, and fluoroquinolones in the 1990s [68,69]. In 2010, 7% of *S.* Typhi infection cases in Malawi were MDR, and this increased to 97% by 2014 [70,71]. In the US, *S.* Enteritidis accounted for 50% of ciprofloxacin-resistant infections, while *S.* Newport, *S.* Typhimurium and *S.* Heidelberg were responsible for 75% of antibiotic-resistant infections as a result of their resistance to ceftriaxone and ampicillin [72]. The resistance of *Salmonella* species to antibiotics is serotype-specific [62].

Novel Antibiotic-Alternatives

Owing to the increase in antibiotic-resistant, AMR, and MDR *Salmonella* serotypes, there is a critical need to develop novel antibiotic alternative approaches to control and treat *Salmonella* infections in humans and animals, including the use of probiotics, prebiotics, and vaccines [73,74].

Probiotics

Probiotics are a group of non-pathogenic microorganisms mainly isolated from fermented dairy products and fecal microbiome that confer health benefits to the host when administered sufficiently [75-77]. For probiotics to be used as therapeutic or prophylactic agents, they have to fulfill specific criteria such as safety margin, efficacy, immunomodulatory capabilities, ability to effectively colonize the intestinal epithelium, resistance to bile salts and low pH, and phenotypic and genetic stability [78]. Probiotics confer health benefits to the host because of their successful competition with pathogens, stimulation of host immune responses, and increased gastrointestinal pH after anaerobic fermentation of carbohydrates [79]. The actions of probiotics include: improving the intestinal barrier and gut mucosal integrity; enhancing intestinal immunity; reducing the colonization of intestinal pathogens; maintaining the balance between pathogenic and beneficial microbes in the gastrointestinal tract; competitive exclusion and secretion of antibacterial substances or metabolites such as bacteriocins that suppress the growth of pathogenic microorganisms; stimulating mucous secretion by intestinal goblet cells to limit epithelial invasion by pathogens; and the production of minerals, enzymes, and trace elements [80-82]. Each probiotic strain has peculiar properties and clinical effects on the host [83], and probiotics can be classified as mono-strain or single-strain probiotics, multi-strain probiotics, and multi-species probiotics [84]. Examples of probiotics include lactobacilli, bifidobacteria, and other lactic acid-producing bacteria (LAB) [46].

Prebiotics

Prebiotics are non-digestible food ingredients which undergo selective fermentation resulting in targeted modifications to the composition and behavior of the gastrointestinal microbiota thereby promoting the growth or activity of a limited number of bacteria in the host colon for the health benefits of the host [47,85]. Prebiotics are considered food ingredients for probiotics including lactobacilli and bifidobacteria as they utilize these ingredients to contribute to the health and well-being of the host, hence, prebiotics are normally combined with probiotics in commercial products since the utility of prebiotics to intestinal bacteria species is essential for providing nutraceutical and nutritional value to the host [46,47]. This combination has great therapeutic efficacy against various animal and human diseases including *Salmonella* infections [47]. Important features of prebiotics include selectivity of microbiota associated with health-promoting effects, resistance to digestion, fermentation by intestinal microbiota, and inducement of biofilm attachment on the epithelial cells of the gut which aids in preventing pathogenic bacteria from adhesion to the gut [86,87]. Herbs and spices are plants with prebiotic qualities which can be used to fortify foods for therapeutic and nutritional purposes against different animal and human diseases worldwide [88]. They help to increase the resistance of hosts to different stresses and increase their absorption of essential nutrients, thus reducing their susceptibility to pathogens [46].

Vaccines

Vaccination is an effective approach to control *Salmonella* infection in humans and animals. *S.* Typhimurium and *S.* Enteritidis account for 70% of all *Salmonella* infection cases in humans associated with eating contaminated food products of poultry origin, mainly meat and eggs, with *S.* Typhimurium being the leading serotype in poultry worldwide followed by *S.* Enteritidis [89]. Both serotypes have significant health consequences for humans worldwide. Hence, intervention through mass vaccination of free from *Salmonella* livestock on farms is a key measure for reducing the prevalence of *Salmonella* in live animals with its implications for food safety. The use of live-attenuated vaccine in livestock can effectively induce protection against bacterial infections as a result of a strong humoral immune response compared to killed vaccine or whole bacteria extract [90]. Live-attenuated *Salmonella* vaccines are preferred as they have a broader host immune response for protection against multiple *Salmonella* serotypes than killed or inactivated vaccines [91]. The rise of antibody titres shortly after vaccination is characteristic of the potent protection against pathogens provided by live-attenuated vaccines in the flock [92]. Vaccination of livestock increases milk productivity, reduces live shedding and intestinal colonization of *Salmonella*, stimulates immune response, protects animals against *Salmonella* infection, and provides healthy animals and food safety benefits [93]. Therefore, vaccinating livestock can prevent the transmission of *Salmonella* infection in humans caused by eating contaminated food products of animal origin. There is currently no approved vaccine against NTS in humans [19,94].

TS (*S.* Typhi and *S.* Paratyphi) have moderately effective vaccines. Live-attenuated oral vaccine Ty21a (Vivotif) and injectable Vi capsular polysaccharide (Vi-CPS) (Typherix or Typhim Vi) vaccine have been designed to induce bacterial lysis and provide cross-protection against both *S.* Typhi and *S.* Paratyphi [95]. Ty21a is genetically stable and prescribed only to children above 5 years of age due to the high dose of vaccine that is required to achieve immunogenicity [96]. A combination of Ty21a and Vi-CPS induces broader protection against *Salmonella* and has proven to be most effective in the America and European countries, while Vi-rEPA is licensed in China to young children against *S.* Typhi [46]. Although vaccines may reduce *Salmonella* infections, its use and effectiveness are however likely to be affected by issues of availability, efficacy, safety, and cost [64].

DISCUSSION

The results of our narrative review identified the following knowledge and research gaps in the pathogenicity, determinants, prevention, control, and treatment of *Salmonella* infections and offered suggestions.

Limited knowledge of the reservoirs, sources, modes of transmission, and risk factors of iNTS:

There is need to improve knowledge of environmental (non-host) risk factors of iNTS infection and to enhance data on host risk factor attribution to iNTS (e.g. HIV/AIDS, malaria, malnutrition, etc.) through community-based studies simultaneously assessing all relevant host risk factors. More information on the prevalence and duration of carriage and shedding of iNTS in humans and other possible reservoirs such as livestock is also required.

Lack of population-based studies of Salmonella infection especially in developing countries:

It is necessary to expand population-based studies of *Salmonella* infection and disease across developing regions like sub-Saharan Africa, and to conduct community-based surveillance (CBS) across these regions. CBS data can serve as important proxies to monitor the impact of interventions (e.g. vaccines or drugs).

Limited data on the serotypes associated with iNTS:

Further research is required on the role and importance of NTS serotypes apart from *S.* Typhimurium and *S.* Enteritidis in causing invasive disease, inclusion as vaccine targets, neonatal meningitis and sepsis associated with maternal iNTS disease, and spread of AMR [97]. Also, it is important to investigate in population-based studies the contribution of NTS strains to natural immunity from gastrointestinal exposure, with or without invasive disease, and the contribution of NTS serotypes not commonly associated with invasive disease to natural immunity [98].

Lack of evidence-based treatment guidelines for iNTS disease:

There are currently no evidence-based treatment for iNTS disease due to lack of data on treatment efficacy. Use of antibiotics is no longer considered standard-of-care due to widespread MDR in circulating iNTS disease-associated strains [99], and there is no human vaccine addressing iNTS disease. Current acceptable treatment for iNTS disease is derived from typhoid fever treatment [100]. Targeted treatment for iNTS is hindered by diagnostic uncertainty, absence of quality assured antimicrobial susceptibility testing, and lack of data on appropriate dose and optimal duration for treatment. Therefore, there is critical need for standardized methods, quality assurance of antimicrobial susceptibility testing, improvement in age-specific antimicrobial formulations, dose calculations, and dosing devices for oral suspension especially among young children.

CONCLUSION

Contaminated food and water predispose individuals to risks of *Salmonella* infection and environmental and socioeconomic factors influence the transmission in both humans and animals. Environmental factors such as poor sanitation and hygiene, inadequate waste and sewage disposal, and lack of access to potable water and socioeconomic factors including poverty, low education, unemployment, high cost of living, overcrowding, and social exclusion are associated with *Salmonella* infection. *S.* Enteritidis and *S.* Typhimurium are the most prevalent NTS serotypes common in both humans and animals, while *S.* Typhi is the most prevalent TS serotype found only in humans. Preventing *Salmonella* contamination of animal products, water, vegetables and fruits, and promoting the safety and quality of foods for animal and human consumption are the primary measures to reduce infections. The increase in antibiotic-resistant *Salmonella* has led to research into novel antibiotic-alternatives to treat *Salmonella* infections through the use of probiotics including lactobacilli, bifidobacteria, and other lactic acid-producing bacteria (LAB); prebiotics such as herbs and spices; and vaccines. Further research is recommended in the treatment of iNTS disease and the development of human vaccine against NTS, as well as in the use other antibiotic-alternatives such as bacteriophages, antimicrobial peptides, organic acids, and essential oils.

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REFERENCES

1. Ngoi ST, Ju Teh CH, Chai LC, Thong KL. Overview of molecular typing tools for the characterization of Salmonella enterica in Malaysia. *Biomed Environ Sci.* 2015;28(10):751-764. doi:10.3967/bes2015.105
2. Majowicz SE, Musto J, Scallan E, *et al*. The global burden of non-typhoidal Salmonella gastroenteritis. *Clin Infect Dis.* 2010;50(6):882-889.
3. de Alwis R, Watson C, Nikolay B, *et al*. Role of environmental factors in shaping spatial distribution of Salmonella enterica serovar Typhi, Fiji. *Emerg Infect Dis.* 2018;24(2):284-293. doi:10.3201/eid2402.170704
4. Centers for Disease Control and Prevention (CDC). Salmonella. CDC; 2022. Accessed May 18, 2022. https://www.cdc.gov/salmo-nella/index.html
5. Haeusler GM, Curtis N. Non-typhoidal Salmonella in children: microbiology, epidemiology and treatment. *Adv Exp Med Biol*. 2013;764:13-26. doi:10.1007/978-1-4614-4726-9_2
6. Christenson J C. Salmonella infections. Pediatrics in Review. 2013;34(9):375-383.
7. Manangazira P, Glavintcheva I, Mutukwa-Gonese G, Bara W, Chimbaru A, Ameda I. (eds). Guidelines for the management of typhoid fever. *World Health Organization.* 2011;1-39
8. Lachlan J. Treatment and prevention methods of Salmonella infection. *J Bacteriol Parasitology.* 2022;13(S19):1-2. doi:10.35248/2155-9597.22.S19.028
9. World Health Organization (WHO). Foodborne disease burden epidemiology reference group 2007-2015. In: WHO Estimates of the Global Burden of Foodborne Diseases. WHO; 2015:1-265.
10. Andino A, Hanning I. Salmonella enterica: survival, colonization, and virulence differences among serovars. *Sci World J*. 2015;2015(1):1-16. doi:10.1155/2015/520179
11. Oludairo OO, Kwaga JKP, Dzikwi AA, Kabir J. The genus Salmonella, isolation and occurrence in wildlife. *Intl J Microbiol Immun Res*. 2013;1(5):47-52.
12. Ryan MP, O'Dwyer J, Adley CC. Evaluation of the complex nomenclature of the clinically and veterinary significant pathogen Salmonella. *BioMed Res Int.* 2017:2017(1):1-6. doi:10.1155/2017/3782182
13. Issenhuth-Jeanjean S, Roggentin P, Mikoleit M, *et al*. Supplement 2008-2010 (no. 48) to the White-Kauffmann-Le Minor scheme. *Res Microbiol.* 2014;165(7):526-530. doi:10.1016/j.resmic.2014.07.004
14. Gal-Mor O. Persistent infection and long-term carriage of typhoidal and nontyphoidal Salmonellae. *Clin Microbiol Rev.* 2019;32(1):1-31. doi:10.1128/CMR.00088-18
15. Eng S-K, Pusparajah P, Ab Mutalib N-S, Ser H-L, Chan K-G, Lee L-H. Salmonella: a review on pathogenesis, epidemiology and antibiotic resistance. *Front Life Sci.* 2015;8(3):284-293. doi:10.1080/21553769.2015.1051243
16. Amenu D. Isolation and characterization of Salmonella from food handlers. *Palgo J Med Medical Sci*. 2016;3(1):42-45.
17. Österberg J. Salmonella in pigs: infection dynamics of different serotypes. Doctoral dissertation. Swedish University of Agricultural Sciences, Uppsala; 2010. Accessed December 12, 2022. https://www.sva.se/media/ffrmk3fj/avhandling_salmonella.pdf
18. Yada EL. A review on: salmonellosis and its economic and public health significance. *Intl J Microbiol Res.* 2023;14(2):21-33. doi: 10.5829/idosi.ijmr.2023.21.33
19. Zizza A, Fallucca A, Guido M, Restivo V, Roveta M, Trucchi C. Foodborne infections and Salmonella: current primary prevention tools and future perspectives. *Vaccines* 2025;13(1):29-48. doi:10.3390/vaccines13010029
20. Xie Z., Zhang Y, Huang X. Evidence and speculation: the response of Salmonella confronted by autophagy in macrophages. *Future Microbiol.* 2020;15(13):1277-1286. doi:10.2217/fmb-2020-0125

21. Soto-Dávila M, Hossain A, Chakraborty S, Rise ML, Santander J. Aeromonas salmonicida subsp. salmonicida early infection and immune response of Atlantic cod (Gadus morhua L.) primary macrophages. *Front Immunol*. 2019;10(1237):1-14. doi:10.3389/fimmu.2019.01237
22. Bula-Rudas FJ, Rathore MH, Maraqa NF. Salmonella infections in childhood. *Adv. Pediatr*. 2015;62(1):29-58. doi:10.1016/j.yapd.2015.04.005
23. Marks F, von Kalckreuth V, Aaby P, *et al*. Incidence of invasive Salmonella disease in sub-Saharan Africa: a multicenter population-based surveillance study. *Lancet Glob Health*. 2017;5(3):e310-323. doi:10.1016/S2214-109X(17)30022-0
24. Gilchrist JJ, MacLennan CA. Invasive nontyphoidal Salmonella disease in Africa. *EcoSal Plus*. 2019;8(2):1-23. doi: 10.1128/ecosalplus.ESP-0007-2018
25. Bornstein K, Hungerford L, Hartley D, *et al*. Modeling the potential for vaccination to diminish the burden of invasive nontyphoidal Salmonella disease in young children in Mali, West Africa. *PLoS Negl Trop Dis.* 2017;11(2):1-19. doi: 10.1371/journal.pntd.0005283
26. Jeon HJ, Pak GD, Im J, *et al*. Determining the best immunization strategy for protecting African children against invasive Salmonella disease. *Clin Infect Dis.* 2018;67(12):1824-1830. doi:10.1093/cid/ciy386
27. Adley CC, Ryan MP. The nature and extent of foodborne disease. In: Barros-Velazquez J., ed. Antimicrobial Food Packaging. Academic Press; 2016:1-10.
28. Alegbeleye O, Sant'Ana AS. Survival of Salmonella spp. under varying temperature and soil conditions. *Sci Total Environ*. 2023;884(2023):1-13. doi: 10.1016/j.scitotenv.2023.163744
29. Kynčl J, Špačková M, Fialová A, Kyselý J, Malý M. Influence of air temperature and implemented veterinary measures on the incidence of human salmonellosis in the Czech Republic during 1998-2017. *BMC Public Health.* 2021;21(55):1-7. doi:10.1186/s12889-020-10122-8
30. Bondo KJ, Pearl, DL, Janecko N. Impact of season, demographic and environmental factors on Salmonella occurrence in raccoons (Procyon lotor) from swine farms and conservation areas in southern Ontario. *PLoS One*. 2016;11(9):1-21. doi: 10.1371/journal.pone.0161497
31. Mehat JW, van Vliet AHM, La Ragione RM. The avian pathogenic Escherichia coli (APEC) pathotype is comprised of multiple distinct, independent genotypes. *Avian Pathol*. 2021;50(5):402-416.
32. Ding M, Li J, Liu X, Li H, Zhang R, Ma, J. Exploring links between water quality and E. coli O157:H7 survival potential in well waters from a rural area of southern Changchun City, China. *J Water Health.* 2017;16(2)300-310. doi:10.2166/wh.2017.162
33. Mirembe BB, Mazeri S, Callaby R, Nyakarahuka L, Kankya C, Muwonge A. Temporal, spatial and household dynamics of Typhoid fever in Kasese district, Uganda. *PLoS One*. 2019;14(4):1-17. doi: 10.1371/journal.pone.0214650
34. Ahmad HA, Akil L. Effects of environment and socioeconomics on Salmonella infections. In: Mares M., ed. Current Topics in Salmonella and Salmonellosis. *Intech;* 2017:235-252. doi:10.5772/67501
35. Mbae C, Mwangi M, Gitau N, *et al*. Factors associated with occurrence of salmonellosis among children living in Mukuru slum, an urban informal settlement in Kenya. *BMC Infect Dis.* 2020;20(422):1-12. doi:10.1186/s12879-020-05134-z
36. Bello AB, Adesola RO, Idris I, Scott GY, Alfa S, Ajibade FA. Combatting extensively drug-resistant Salmonella: a global perspective on outbreaks, impacts, and control strategies. *Pathog Glob Health.* 2024;118(7-8):559-573. doi:10.1080/20477724.2024.2416864
37. Ayuti SR, Khairullah AR, Al-Arif MA, *et al*. Tackling salmonellosis: a comprehensive exploration of risks factors, impacts, and solutions. *Open Vet J*. 2024;14(6):1313-1329. doi: 10.5455/OVJ.2024.v14.i6.1
38. Clasen T. Household water treatment and safe storage to prevent diarrheal disease in developing countries. *Curr Environ Health Rep*. 2015;2(1):69-74. doi:10.1007/s40572-014-0033-9
39. Rosa G, Kelly P, Clasen T. Consistency of use and effectiveness of household water treatment practices among urban and rural populations claiming to treat their drinking water at home: a case study in Zambia. *Am J Trop Med Hyg*. 2016;94(2):445-55. doi:10.4269/ajtmh.15-0563
40. Wierup M. The importance of hazard analysis by critical control point for effective pathogen control in animal feed: assessment of Salmonella control in feed production in Sweden, 1982-2005. *Foodborne Pathog Dis*. 2023;20(12)545-552. doi:10.1089/fpd.2023.0067
41. Osimani A, Aquilanti L, Clementi F. Salmonellosis associated with mass catering: a survey of European Union cases over a 15-year period. *Epidemiol Infect*. 2016;144(14)3000-3012. doi:10.1017/S0950268816001540
42. Balasubramanian R, Im J, Lee J-S, Jeon HJ, Mogeni OD, Kim JH, *et al*. The global burden and epidemiology of invasive non-typhoidal Salmonella

infections. *Hum Vaccin Immunother*. 2019;15(6):1421-1426. doi.10.1080/21645515.2018.1504717
43. Galipó E, Zoche-Golob V, Sassu EL, *et al*. Prioritization of pig farm biosecurity for control of Salmonella and hepatitis E virus infections: results of a European expert opinion elicitation. *Porc. Health Manag.* 2023;9(8):1-13. doi:10.1186/s40813-023-00306-0
44. Renault V, Damiaans B, Sarrazin S, Humblet MF, Dewulf J, Saegerman C. Biosecurity practices in Belgian cattle farming: level of implementation, constraints and weaknesses. *Transbound. Emerg Dis.* 2018;65(5)1246-1261. doi:10.1111/tbed.12865
45. Van Limbergen T, Dewulf J, Klinkenberg M, *et al*. Scoring biosecurity in European conventional broiler production. *Poult Sci.* 2018;97(1):74-83. doi:10.3382/ps/pex296
46. Mkangara M. Prevention and control of human Salmonella enterica infections: an implication in food safety. *Int J Food Sci*. 2023;2023(8899596):1-26. doi:10.1155/ 2023/8899596
47. Lamichhane B, Mawad AMM, Saleh M, *et al*. Salmonellosis: an overview of epidemiology, pathogenesis, and innovative approaches to mitigate the antimicrobial resistant infections. *Antibiotics.* 2024;13(76):1-51. doi:10.3390/antibiotics13010076
48. Course CE, Boerlin P, Slavic D, Vaillancourt J-P, Guerin MT. Factors associated with Salmonella enterica and Escherichia coli during downtime in commercial broiler chicken barns in Ontario. *Poult Sci.* 2021;100(5):1-16. doi: 10.1016/j.psj.2021.101065
49. Tilli G, Laconi A, Galuppo F, Mughini-Gras L, Piccirillo A. Assessing biosecurity compliance in poultry farms: a survey in a densely populated poultry area in North East Italy. *Animals*. 2022;12(11):1409-1417 doi:10.3390/ani12111409
50. Liu H, Whitehouse CA, Li B. Presence and persistence of Salmonella in water: the impact on microbial quality of water and food safety. *Front Public Health.* 2018;6(159):1-13. doi:10.3389/fpubh.2018.00159
51. Butucel E, Balta I, McCleery D, *et al*. Farm biosecurity measures and interventions with an impact on bacterial biofilms. *Agriculture.* 2022;12(8):1251-1269. doi:10.3390/agriculture12081251
52. Tomičić Z, Čabarkapa I, Čolović R, Đuragić O, Tomičić R. Salmonella in the feed industry: problems and potential solutions. *J Agron Technol Eng Manag*. 2019;2(1):130-137.
53. Lamas A, Miranda JM, Regal P, Vázquez B, Franco CM, Cepeda A. A comprehensive review of non-enterica subspecies of Salmonella enterica. *Microbiol Res.* 2018;206(4):60-73. doi: 10.1016/j.micres.2017.09.010
54. Humam AM, Loh TC, Foo HL, *et al*. Effects of feeding different postbiotics produced by Lactobacillus plantarum on growth performance, carcass yield, intestinal morphology, gut microbiota composition, immune status, and growth gene expression in broilers under heat stress. *Animals.* 2019;9(9):644-663. doi:10.3390/ani9090644
55. Rasschaert G, Michiels J, Tagliabue M, Missotten J, De Smet S, Heyndrickx M. Effect of organic acids on Salmonella shedding and colonization in pigs on a farm with high Salmonella prevalence. *J Food Prot.* 2016;79(1):51-58. doi: 10.4315/0362-028X.JFP-15-183
56. Ehuwa O, Jaiswal AK, Jaiswal S. Salmonella, food safety and food handling practices. *Foods.* 2021;10(5):907-922. doi:10.3390/foods10050907
57. Awuchi CG. HACCP, quality, and food safety management in food and agricultural systems. *Cogent Food Agric.* 2023;9(1):1-29. doi:10.1080/23311932.2023.2176280
58. Uelze L, Becker N, Borowiak M, *et al*. Toward an integrated genome-based surveillance of Salmonella enterica in Germany. *Front Microbiol*. 2021;12(626941):1-13. doi:10.3389/fmicb.2021.626941
59. Arya G, Holtslander R, Robertson J, *et al*. Epidemiology, pathogenesis, genoserotyping, antimicrobial resistance, and prevention and control of non-typhoidal Salmonella serovars. *Curr Clin Microbiol Rep.* 2017;4(1):43-53. doi:10.1007/s40588-017-0057-7
60. Ferrari RG, Rosario DKA, Cunha-Neto A, Mano SB, Figueiredo EES, Conte-Junior CA. Worldwide epidemiology of Salmonella serovars in animal-based foods: a meta-analysis. *Appl Environ Microbiol.* 2019;85(14):1-21. doi:10.1128/AEM.00591-19
61. Smith SI, Seriki A, Ajayi A. Typhoidal and non-typhoidal Salmonella infections in Africa. *Eur J Clin Microbiol Infect Dis.* 2016;35(112):1913-1922. doi:10.1007/s10096-016-2760-3
62. Medalla F, Gu W, Mahon BE, *et al*. Estimated incidence of antimicrobial drug-resistant nontyphoidal Salmonella infections, United States, 2004-2012. *Emerg Infect Dis*. 2016;23(1):29-37. doi:10.3201/eid2301.160771
63. Feasey NA, Everett D, Faragher EB, *et al*. Modelling the contributions of malaria, HIV, malnutrition and rainfall to the decline in paediatric invasive non-typhoidal Salmonella disease in Malawi. *PLoS Negl Trop Dis*.

2015;9(7):1-12. doi: 10.1371/journal.pntd.0003979

64. Kumar P, Kumar R. Enteric fever. *Indian J Pediatr* 2017;84(3):227-230. doi:10.1007/s12098-016-2246-4
65. Crump JA, Sjölund-Karlsson M, Gordon MA, Parry CM. Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance, and antimicrobial management of invasive Salmonella infections. *Clin Microbiol Rev*. 2015;28(4):901-937. doi:10.1128/CMR.00002-15
66. Nami Y, Haghshenas B, Abdullah N, *et al*. Probiotics or antibiotics: future challenges in medicine. *J Med Microbiol.* 2015;64(2):137-146. doi:10.1099/jmm.0.078923-0
67. Sabtu N, Enoch DA, Brown NM. Antibiotic resistance: what, why, where, when and how? *Br Med Bull.* 2015;116(1):105-113. doi:10.1093/bmb/ldv041
68. Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL. Typhoid Fever. *Lancet*. 2015;385(9973):1136-1145. doi:10.1016/S0140-6736(13)62708-7
69. Baltazar M, Ngandjio A, Holt KE, *et al*. Multidrug-resistant Salmonella enterica Serotype Typhi, Gulf of Guinea Region, Africa. *Emerg Infect Dis.* 2015;21(4):655-659. doi:10.3201/eid2104.141355
70. Feasey NA, Gaskell K, Wong V, *et al*. Rapid emergence of multidrug-resistant, H58-lineage Salmonella typhi in Blantyre, Malawi. *PloS Negl Trop Dis.* 2015;9(4):1-13. doi: 10.1371/journal.pntd.0003748
71. Wong VK, Baker S, Pickard DJ, *et al*. Phylogeographical analysis of the dominant multidrug-resistant H58 clade of Salmonella typhi identifies inter- and intracontinental transmission events. *Nat Genet.* 2015;47(6):632-639. doi:10.1038/ng.3281
72. Gut AM, Vasiljevic T, Yeager T, Donkor ON. Salmonella infection - prevention and treatment by antibiotics and probiotic yeasts: a review. *Microbiology.* 2018;164(11):1327-1344. doi:10.1099/mic.0.000709
73. Mancini F, Micoli F, Necchi F, Pizza M, Berlanda Scorza F, Rossi O. GMMA-based vaccines: the known and the unknown. *Front Immunol.* 2021;12(715393):1-7. doi:10.3389/fimmu.2021.715393
74. Łojewska E, Sakowicz T. An alternative to antibiotics: selected methods to combat zoonotic foodborne bacterial infections. *Curr Microbiol.* 2021;78(12)4037-4049. doi:10.1007/s00284-021-02665-9
75. Alagawany M, Abd El-Hack ME, Farag MR, Sachan S, Karthik K, Dhama K. The use of probiotics as eco-friendly alternatives for antibiotics in poultry nutrition. *Environ Sci Pollut Res Int*. 2018;25(11)10611-10618. doi:1007/s11356-018-1687-x
76. Cunningham M, Azcarate-Peril MA, Barnard A, *et al*. Shaping the future of probiotics and prebiotics. *Trends Microbiol*. 2021;29(8):667-685. doi: 10.1016/j.tim.2021.01.003
77. Helmy YA, Taha-Abdelaziz K, Hawwas HAE, *et al*. Antimicrobial resistance and recent alternatives to antibiotics for the control of bacterial pathogens with an emphasis on foodborne pathogens. *Antibiotics*. 2023;12(2):274- . doi:10.3390/antibiotics12020274
78. de Melo Pereira GV, de Oliveira Coelho B, Magalhães Júnior AI, Thomaz-Soccol V, Soccol, CR. How to select a probiotic? a review and update of methods and criteria. *Biotechnol Adv.* 2018;36(8)2060-2076. doi: 10.1016/j.biotechadv.2018.09.003
79. Ranjha MMAN, Shafique B, Batool M, *et al*. Nutritional and health potential of probiotics: a review. *Appl Sci.* 2021;11(23):11204-2021. doi: 10.3390/app112311204
80. Liu D, Jiang X-Y, Zhou L-S, Song J-H, Zhang X. Effects of probiotics on intestinal mucosa barrier in patients with colorectal cancer after operation: meta-analysis of randomized controlled trials. *Medicine*. 2016;95(15):1-14. doi:10.1097/MD.0000000000003342
81. Alizadeh M, Bavananthasivam J, Shojadoost B, *et al*. In ovo and oral administration of probiotic lactobacilli modulate cell- and antibody-mediated immune responses in newly hatched chicks. *Front Immunol*. 2021;12(664387):1-13. doi: 10.3389/fimmu.2021.664387
82. Kulkarni RR, Gaghan C, Gorrell K, Sharif S, Taha-Abdelaziz K. Probiotics as alternatives to antibiotics for the prevention and control of necrotic enteritis in chickens. *Pathogens.* 2022;11(6):692-711. doi:10.3390/pathogens11060692
83. Stavropoulou E, Bezirtzoglou E. Probiotics in medicine: a long debate. *Front Immunol.* 2020;11(2192):1-20. doi:10.3389/fimmu.2020.02192
84. Wang Y-C, Hu S-Y, Chiu C-S, Liu C-H. Multiple-strain probiotics appear to be more effective in improving the growth performance and health status of white shrimp, Litopenaeus vannamei, than single probiotic strains. *Fish Shellfish Immunol.* 2019;84:1050-1058. doi: 10.1016/j.fsi.2018.11.017
85. Hutkins RW, Krumbeck JA, Bindels LB, *et al*. Prebiotics: why definitions matter. *Curr Opin Biotechnol.* 2016;37:1-7. doi: 10.1016/j.copbio.2015.09.001
86. Rashidinejad A, Bahrami A, Rehman A, *et al*. Co-encapsulation of probiotics with prebiotics and

their application in functional/synbiotic dairy products. *Crit Rev Food Sci Nutr.* 2022;62(9):2470-2494. doi: 10.1080/10408398.2020.1854169

87. Tran THT, Everaert N, Bindelle J. Review on the effects of potential prebiotics on controlling intestinal enteropathogens Salmonella and Escherichia coli in pig production. *J Anim Physiol Anim Nutr,* 2018;102(1):17-32. doi:10.1111/jpn.12666
88. Mostafa AA, Al-Askar AA, Almaary KS, Dawoud TM, Sholkamy EN, Bakri MM. Antimicrobial activity of some plant extracts against bacterial strains causing food poisoning diseases. *Saudi J Biol Sci.* 2018;25(2):361-366. doi: 10.1016/j.sjbs.2017.02.004
89. Chang Y. Bacteriophage-derived endolysins applied as potent biocontrol agents to enhance food safety. *Microorganisms.* 2020;8(5):724-734. doi:10.3390/micoorganisms8050724
90. Shah DH, Paul NC, Sischo WC, Crespo R, Guard J. Population dynamics and antimicrobial resistance of the most prevalent poultry-associated Salmonella serotypes. *Poultry Sci,* 2017;96(3):687-702. doi:10.3382/ps/pew342
91. Rabie NS, Amin Girh ZMS. Bacterial vaccines in poultry. *Bull Natl Res Cent.* 2020;44(15):1-7. doi:10.1186/s42269-019-0260-1
92. Jia S, McWhorter AR, Andrews DM, Underwood GJ, Chousalkar KK. Challenges in vaccinating layer hens against Salmonella Typhimurium. *Vaccines.* 2020;8(4):696-707. doi:10.3390/vaccines8040696
93. Wales AD, Davies RH. Salmonella vaccination in pigs: a review. *Zoonoses Public Health*. 2017;64(1):1-13. doi:10.1111//zph.12256
94. Martin, LB, Tack B, Marchello CS, *et al*. Vaccine value profile for invasive non-typhoidal Salmonella disease. *Vaccine*. 2024;42(19S1):S101-S124. doi: 10.1016/j.vaccine.2024.04.045
95. Mukhopadhyay B, Sur D, Gupta SS, Ganguly NK. Typhoid fever: control & challenges in India. *Indian J. Med. Res.* 2019;150(5):437-447. doi: 10.4103/ijmr.IJMR_411_18
96. Amicizia D, Arata L, Zangrillo F, Panatto D, Gasparini R. Overview of the impact of typhoid and paratyphoid fever. Utility of Ty21a vaccine (Vivotif®). *J Prev Med Hyg.* 2017;58(1):E1-E8. doi:10.15167/2421-4248/jpmh2017.58.1.747
97. Hagedoorn NN, Murthy S, Birkhold M, Marchello CS, Crump JA; Vacc-iNTS Consortium Collaborators. Prevalence and distribution of non-typhoidal Salmonella enterica serogroups and serovars isolated from normally sterile sites: a global systematic review. *Epidemiol Infect.* 2023;152(e4):1-8 doi:10.1017/S0950268823001693
98. Gilchrist JJ, MacLennan CA, Hill AVS. Genetic susceptibility to invasive Salmonella disease. *Nat Rev Immunol.* 2015;15(7):452-463. doi:10.1038/nri3858
99. Feasey NA, Masesa C, Jassi C, *et al*. Three epidemics of invasive multidrug-resistant Salmonella bloodstream infection in Blantyre, Malawi, 1998-2014. *Clin Infect Dis.* 2015;61(Suppl 4):S363-S371. doi:10.1093/cid/civ691
100. Blumentrath CG, Müller G, Teichmann D, Tiesmeier J, Petridou J. Relapse of typhoid fever following delayed response to meropenem: a case report and review of previously published cases indicating limited clinical efficacy of meropenem for the treatment of typhoid fever. *Ger Med Sci*. 2019;17(1):1-9. doi:10.3205/000267