Salmonella Resistance in Broiler Chicken: Risk to Human Health

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ABSTRACT

Salmonella is the most common zoonotic foodborne pathogen of economic status in animals and humans. The natural habitat of Salmonella is the gastrointestinal tract (GIT) of domestic and wild animals, part of diverse foodstuffs of both animal and plant origin, that become infected directly or indirectly with Salmonella. Most domestic and wild animals are infected with Salmonella spp. with no signs of illness. Due to increasing antibiotic resistance of Salmonella, poultry food and feedstuff became the main source of infection for humans. Appropriate risk analysis and effective control measures could reduce the prevalence of Salmonellosis at production and processing sites, that eventually, improves human health and be beneficial for mankind.

Keywords: Salmonella; Animals; Humans; Foodstuff; Poultry; Antibiotic resistance

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1. INTRODUCTION

Animal proteins are the most demanded protein source around the World, accepted by different faith groups. Whereas, poultry meat is considered as the most consumed and economic meat among animal sources. In recent years, poultry meat consumption increased by 5.5% per capita worldwide, indicating the demand for this product for protein availability and food security (Machado Junior et al. 2020). Nonetheless, consumption of contaminated poultry products (meat, egg) was stated to induce 20.6% foodborne diseases in the United States from 1998 to 2008, in which *Salmonella* spp. was one of the main etiological agents (Painter et al. 2013). *Salmonella* natural habitat is GIT of birds and, can be entered into the production system by contaminated water or feed, litter, live vectors and even through human contaminated tools and boots etc. (Wales et al. 2010). Contaminated poultry meat and eggs are considered as the main risk for human infections. Early, incorporation of antibiotics was considered as the greatest solution to get rid of such zoonotic pathogenic bacteria, but later, with emergence of antibiotic resistant *Salmonella* outbreaks changed the vision.

Risk analysis and modelling frameworks were carried out to evaluate and define control measures for the risk of food borne diseases cause by *Salmonella* from layers (Namata et al. 2008), broilers (Namata et al. 2009; Rajan et al. 2017; Kloska et al. 2017), dairy cattle (Nielsen and Nielsen 2012), and pigs (Binter et al. 2011; Hill et al. 2016). Surveillance, vaccination and biosecurity have been associated to ultimate decline in salmonellosis, so, need to focus and put more efforts on serotypes, cause incidence of disease in humans such as *Salmonella typhimurium* and *Salmonella enteritidis* by adopting efficient control measures in poultry and egg production (Hugas and Beloeil 2014). At both processing plants and production site, simple hygiene practices could eliminate and prevent contamination of such pathogenic microorganisms (Hugas and Beloeil 2014).

Poultry food safety requires appropriate management at each level of processing and production in such a way that active antimicrobials can be applied. Steps should be taken to evaluate microbial testing and data analysis for *Salmonella* positive forms and precautionary measures should be adopted to avoid cross contamination. Once the problem, risks associated with execution of the problem, possible solution and their implementation are strategically defined, then application of such solutions are validated and applied for the next step. It is very important that these antimicrobial implementations be validated at that step they are applied and as part of overall food safety. In addition to these antimicrobials, feed additives which generate a positive effect on overall health of animals should be adopted in order to generate safer and up to the mark of standard and quality food and feedstuff. Such food safety practices should be implemented, understood and communicated throughout the poultry production and processing continuum.

2. HISTORY OF *SALMONELLA*

The bacterium *Salmonella* was first found by Soholerin in 1839 (Myruvik et al. 1976), and isolated from a person who died from typhoid fever by Eberth in 1880 from the tissues of spleen and mesenteric lymph nodes. Later, in 1888 was cultured by Smith and Salmon from a pig, perished from hog cholera (Merchant and Packer 1977). Later in 1888, Garter carried out its isolation in human (Bryan et al. 1979). However, the major contribution in isolation of Salmonella was by White Kaufmann-Le Minor, out of 2600 serotypes 1600 of which belongs to *S. enterica*. Over 200 serotypes are reported to cause disease in humans (Xu et al. 2021).

For over a century, foodborne infections have been major health concerns that *Salmonella* instigated (Worku et al. 2022) and are grouped as typhiodal salmonellosis (TS, commonly called enteric fever) and non-typhoidal salmonellosis (NTS, commonly called gastroenteritis) infections (Ngogo et al. 2020; Akinyemi et al. 2021). Typhoid fever is caused by *Salmonella enterica* serovar *typhi* while the para-typhoid fever is caused by *Salmonella paratyphi* A, B and C (Akinyemi et al. 2021). While the source of NTS infection is group of *S. enterica* serovars *S. typhimurium, S. enteriditis* and *S. cholerasuis*, these are responsible serovars that cause infection in individuals through consumption of contaminated food products and diets (Thung et al. 2018).

3. CLASSIFICATION OF SALMONELLA SPECIES

Salmonella is a genus categorized in the family Enterobacteriacae, which retain thought-provoking genotypic and phenotypic characteristics with peculiar nomenclature compared to bacteria of same and outside the family (Oludairo et al. 2022). The classification of *Salmonella* remained controversial and multifaceted (Euzeby 1999). According to most accepted nomenclature, based on variation in the sequence of the 16Sr RNA gene, this genus comprises of two major species *Salmonella enterica* and *Salmonella bognori* (Crump et al. 2011; Dione et al. 2011). Depending on the geographic distribution, host adaptations, antigenic nature, biochemical reaction and DNA-relatedness the S. enterica is further categorized in six sub-species (Carter and Wise 2004). These were S. enterica enterica (I), *S. enterica salamae* (II), *S. enterica arizonae* (IIIa) *S. enterica diarizonae* (IIIb), *S. enterica houtenae* (IV) and *S. enterica indica* (VI).

While the *S. bognori*, most commonly occurs in cold-blooded animals and surroundings (Brenner et al. 2000). Seventeen serovars are identified and represented with symbol V (Jordain and Pattison 1996; Lake et al. 2002). Among all, serovars of subspecies I (S. enterica) are highly pathogenic although other subspecies and *S. bongnori* are relatively less infectious to animals and humans (Lake et al. 2002; Rahman and Othman 2017).

Salmonella is classified into three species according to the biochemical characteristics of the genus, that includes, *S. Choleraesuis* with only one serovar and specific host is swine, *S.typhi* also have one serovar and it mainly infect humans. While, the third *S. enteritidis* contains about 2000 serovars and it includes all serovars that infect animal and human (Carter and Wise 2004). According to host predilection *Salmonella* can also be divided in three groups: adapted to man S. typhi and *S. paratyphi*, adapted to most of the animals *S. choleraesuis* and serovars of *S. enteritidis* while the third have all the serotypes that are not adapted to particular host. New serotypes are frequently identified and added to many previously classified (Rahman and Othman 2017).

4. *SALMONELLA* OUTBREAKS

Zoonotic outbreaks are when individuals abide from the same diseases from animals, animal products and associated environment (EFSA 2021; Abebe et al. 2020). *Salmonella* grounds for diverse diseases i.e., enteritis, septicemia and abortion, while rarely in less than 1% of clinical cases meningitis is also reported (Gille-Johnson et al. 2000; Koonse et al. 2005). These diseases show less specificity for their host species (Gopee et al. 2000; El-Sharkawy 2017).

In numerous regions of the world, salmonellosis is among the most substantial public health challenges (Padungtod and Kaneene 2006; Vindigni et al. 2007). Occurrence also have been reported in southern Thailand from poultry and eggs (Lertworapreecha et al. 2013), while in USA and Europe from meat and beef (Yavari 2012; Heredia and Garcia 2018). Lecis et al (2011) studied the incidence of Salmonella in fresh milk, pork and chocolate in Europe and parts of Africa. Epidemics have also been reported in Africa, Europe and USA from insects and wildlife in (Hidalgo-Vila et al. 2007; Percipalle et al. 2011; Heredia and Garcia 2018).

In Africa Non-typhi *Salmonella* appeared to be endemic and a major cause of bacteremia with 4100 deaths per year mostly in children (Majowicz et al. 2010). As in South and Eastern Africa *Salmonella typhi* is the foremost source of bloodstream infections with multiple outbreaks since 2012 (N'cho 2019). Very high incidence was reported in Malawi 444 cases per 100,000 person per year (Meiring et al. 2021). Among the most common serotypes were *Salmonella enteritidis* and typhimurium was reported as a common cause of iNTS (Feasey et al. 2015). In a case study on children from Kenya indicated 1.3% bloodstream infections were caused by *S. typhimurium* and *S. enteriditis* while *Salmonella typhi* caused its 1.4% (Mbae et al. 2020). Worrisome rising trend in NTS cases was reported from the Middle East and Northern Africa as Sudan 9.2% Tunisia 10.2%, and highest in Morroco was 17.9%. Whereas the lowest were reported in Oman 1.2%, Palestine 1.2 % and Jordon 1.1%. (Andrews-Polymenis 2014; Fardsanei et al. 2018; Al-Rifai et al. 2019). In Saudi Arabia, the *Salmonella* based infections become predominant during Umrah and Hajj season (Abd El Ghany et al. 2017).

In the United States of America, a report by CDC (Centers for Disease Control and Prevention) estimated 1.35 million illnesses in 2022, in which 26,500 hospitalizations and 420 deaths occur due to NTS infections each year (Kuehn 2019). In late 2022, because of *Salmonella typhimurium* a multi-country outbreak was reported in the US and UK. In 2014 Salmonellosis remained the second most communal zoonotic disease in the European Union (EU) with the incidence of 9830 hospitalizations and 65 fatalities in humans (ECDC 2015). However, a stability in infection was observed from 2015-2019 but a considerable decrease was reported in the year 2020 (EFSA 2021). In China it was reported in 2015 that outbreaks of food-borne diseases Salmonella were the second most common pathogen (Fu et al. 2019). He et al. 2023 reported the Salmonella infections from 2012-2021 in Zhejiang province with 1614 hospitalizations among 11,269 cases, when the average positive rate was 3.65% for the entire province.

Infections instigated by *S. typhimurium* impose serious health concerns in low and middle-income countries including Pakistan (WHO 2017). Where the residents of Punjab and Sindh provinces were most vulnerable to infections among the all the disease prevailing Asian nations (Rasheed et al. 2019). A study reported in 2018 that *S. Typhi* infections were also on a higher rate in Pakistan among all the south East Asian countries (Watkins et al. 2020). As in Sindh province first large-scale outbreak, 493.5 cases were reported among 100,000 population (Klemm et al. 2018; Fatima et al. 2021), while in Punjab reports were similar (Saeed et al. 2020; Kim et al. 2021; Nizamuddin et al. 2021) as well as among international travellers (Godbole et al. 2018; Chirico et al. 2020; Watkins et al. 2020). Outbreaks of a new subvariant of extensively drug resistance (XDR) *S. typhi* emerged in Pakistan in the province Sindh (WHO 2019). From September 2020, 2883 were reported, the pervasiveness increased from 7 to 15 per 100,000 people per year. Now this lineage is spreading beyond the province (Ahmad et al. 2021; Rashid et al. 2023).

5. ROUTES OF TRANSMISSION-SALMONELLOSIS

Primary reservoir of Salmonella in human and animals are gastro intestinal tract (GIT), nonetheless there is wide range of sources of Salmonella infections i.e., egg, meat, dairy products, vegetables and water (Brenner et al. 2000). Food is the most common source of infection in developed countries and food-borne infections are difficult to identify, while it is the most imperative measure to prevent the infections also (Shi et al. 2015). In Australia 70% increased cases were reported between 2000-2013, in which food was a source relating both Salmonella *typhi* and Salmonella non-typhi (Pires et al. 2014). Water might signify a source of contamination while the egg and meat remain the most important source (Ford et al. 2016). The acquisition of the infection has been associated with exposure with the chicken and other birds can carry microorganisms (Seif et al. 2019). After contact with pets' infection has also been reported, while person to person transmission is also possible (Gut et al. 2018). In China, a multidrug resistant species (MDR) was identified from livestock in several provinces (Kuang 2015; Wang et al. 2020)

Some serotypes are host specific as *S. typhi* only infects humans while others to warm-blooded animals. Around 50 serovars are tangled in the incidence of disease in humans and animals (Ford et al. 2016).

6. EFFECT OF *SALMONELLA* ON HEALTH OF BROILER CHICKEN

Salmonella pass in the host through oral route, and colonizes inside the alimentary canal. Though, it is normally spread by poultry meat and egg shell contamination *via* chicken intestinal innards (Pires et al. 2014). The numeral laying hens placed in cage free systems upsurges the risk of *Salmonella* contamination in egg feces, because eggs are in close contact to chicken's dropping (Whiley and Ross 2015).
Although, *Salmonella enteritidis* follow two main paths of egg contamination;

- Horizontal Transmission
- Vertical Transmission

Horizontal transmission or indirect infection; eggs can be infected by contaminated droppings during or after laying eggs or dissemination over eggshell from the colonized chicken gut (De Reu et al. 2006).
Vertical transmission or direct infection; infestation to eggshells before egg laying, eggshell membranes, albumin, egg yolk or instigating *Salmonella enteritidis* infection to reproductive organs (Wibisono et al. 2020).
Salmonella infection spreads in poultry either horizontal or vertical mode of transmission and its prevalence is greater in 1-day old chicks. Grownup birds are less susceptible to Salmonellosis (Shivaprasad et al. 2013). Severity of the disease depends upon the age of the bird. Younger the bird, the more severe the impact. Besides this, severity of salmonellosis in broiler chicken differs according to various factors in different avian species that includes environmental stress, presence of coinfections, hostage, host immunity, infective dose and management factors etc. (Wibisono et al. 2020). Mainly, *Salmonella* infecting avian species by two ways; *Salmonella gallinarum* and *Salmonella pullorum*. Therefore, Center for Disease Control and Prevention (CDC) also reported the infection from low avian specific serovars for example, *S. Kentucky*, *S. lille*, *S.berta*, *S.anatum*, *S. infantis*, S.*berta*, *S. javiana, S.newport* and *S. eneteritidis* (CDC 2013a; CDC 2013b).
Gram negative bacteria, Salmonella enters the host, through oral route and colonize in the Sgastrointestinal tract. There are numerous factors associated Salmonella colonization in poultry includes;

- Age of the chicken
- Survival of *Salmonella* across gastric barrier
- Diet
- Physiological and environmental stressors
- Animal health and disease status
- Genetic background of the bird
- Usage of antimicrobials and coccidiostats (Dunkley et al. 2008)

So, *S. enteritidis* is habituated to the intestinal villi and colonized in the GIT with the help of the protein, known as adhesions (Beachey 1981). To avoid bacterial infection, the most common method is to avoid it from binding to intestinal epithelial cell receptors (Wizemann et al. 1999). In poultry, macrophages and heterophils, innate immunity cells play a significant role in intestinal infection (Fasina 2010). As the pathogen enters into the host intestinal epithelial barrier, innate immunity cells move to the site *via* oxidative stress and phagocytosis destroy such pathogens (Brisbin et al. 2008). Salmonellosis in chicken increases significantly in inflammatory cytokines such as IL-1β, INF-g and LITAF (Matulova et al. 2013). Though, *Salmonella* disables host defense by collecting IL-10, a suppressive cytokine.
However, adaptive immune response includes humoral and cell-mediated response for *Salmonella* infection. Though, first adaptive immune response against *S. enteritidis* infection is through the mucosal immune system, involving mucosal associated leukocytes and lymphocytes production and mucosal immunoglobulin A (IgA) (Wigley 2014). These mucosal immunoglobulins A inhibits *S. enteritidis* from attachment to intestinal epithelial cells, and prevents mucosal colonization (Wigley 2014). Shape of the intestine is a decisive factor of intestinal health. Due to increased surface area and decreased tissue

turnover rate, enhanced villus height and reduced crypt depth parallel with excessive nutrient absorption within the small intestine (Munyaka et al. 2012). In contrast, Chicks infested by *S. typhimurium* showed reduced jejunal villus height, crypt depth and height: crypt depth ratio subsequently results in severe enteritis (Borsoi et al. 2011).

7. *SALMONELLA* RESISTANT IN BROILER CHICKEN

Flemming discovered the first antibiotic called Penicillin in 1928 (Fairley 2007) that greatly reduced the mortality and morbidity during World War II in 1940's. Antibiotics are effective chemical substances to treat patients with bacteria causing infectious diseases (Saylers and Whitt 2005). Antibiotics reproduce their effects either bacteriostatic or bactericidal ways (Croft et al. 2007). Antibiotics are collectively referred to as antimicrobial agents to compounds produced by numerous microorganisms, drugs, synthetic chemicals, disinfectants etc. (Saylers and Whitt 2005). Although, antibiotics lose their efficacy as resistance provokes. Antimicrobial resistance may be intrinsically acquired by exchange of DNA fragment (Croft et al. 2007). Such mutations occur over spontaneous mutation, can be frameshift mutation, point mutation, insertion of large element and deletion of genetic material, naturally taking place with average rate of 1×10^{-6} base pairs exchange of genetic material from other bacteria. This way bacteria acquire adaptation to confront against the deadly effects of antimicrobial agents.

Mechanisms of bacterial resistance vary among different species of bacteria. Bacteria have the remarkable ability to survive. As far as, *Salmonella* is concerned, 3 different methods are elucidated to show antimicrobial resistance;

- By producing specific proteins, in the form of enzymes, which digest and alters the antimicrobial into no longer effective e.g., *Salmonella* β-lactamases inactivates β-lactam class (Croft et al. 2007; Cosby et al. 2015).
- By inducing an efflux pump that effectively pumps antimicrobial out of bacterial cell, such as, antimicrobial conc. inside the cell not approach to threshold to interfere with cell metabolic processes e.g., Chloramphenicol and tetracyclines resistance in *Salmonella* spp. (Foley and Lynne 2008)
- By mutating the target or produce chemical change to target site on which antimicrobial insert effects, known as receptor modification e.g., vancomycin resistant enterococci cause mutation on receptor site induce low affinity to vancomycin (Croft et al. 2007; Cosby et al. 2015)

However, other factors for the development of resistance include inability to detect new phenotypes, multiplication of different clones and selective pressure. Selective pressure commensurate by overuse of antibiotics for treatment of human diseases and in-home disinfectants (Rybak 2004)

Two basic methods for transmission of antimicrobial resistance implemented in *Salmonella*.

- Antimicrobial drug resistant *Salmonella* isolates clonal spread
- Horizontal transfer of antibiotic resistance genes (Molbak et al. 1999; Butaye et al. 2006)

Horizontal transfer of resistance genes could be easily transferred from one strain of *Salmonella* to another or among another bacterium spp. (Guerra et al. 2002). In case of *Salmonella*, Class I integrons and plasmids principally involved in horizontal transfer (Guerra et al. 2002; Dieye et al. 2009). Integrons, genetic determinants of machineries of site-specific recombination systems that establish mobile gene cassettes. Though, Class I and Class II integrons have been found in *Salmonella*; Class I represents resistance integrons, are mainly in the *Salmonella* genomic islands, Class II integrons presents super-integrons, related to TN7 transposon family, not yet fully explained (Carattoli 2003; Fluit 2005).

8. *SALMONELLA* ANTIMICROBIAL RESISTANCE AGAINST ANTIMICROBIAL CLASSES

Antimicrobial resistance develops when microorganisms develop such mechanisms to protect themselves from the antimicrobial drugs, used to cure the infection, induced by such pathogens (Cosby et al. 2015).

8.1. TETRACYCLINE

About 31 antimicrobials along with tetracycline approved by the United States of America in 1951, for use in broiler feed, deprived of any veterinary prescription for the animal growth and production and treatment of coccidiosis (Jones and Ricke 2003). Though, in the late 1960s, each European state passed its own National regulations for the antibiotics use in animal feed (Castanon 2007). Broilers that survived at 35 days of age, developed antibiotics resistance (Diarra et al. 2007). As an antimicrobial, tetracycline inhibits protein synthesis by preventing attachment of tRNA to A site of 30S ribosomal subunit. Salmonella isolates ascribed to the energy dependent efflux pump that potentially eliminates tetracycline from bacterial cells. Another mechanism of antimicrobial resistance reported in other bacterial spp., not in *Salmonella* (Chopra and Robberts 2001). Almost 32 genes are reported that are involved in tetracycline and oxytetracycline resistance such as *tet(A)*, *tet(B)*, *tet(C)*, *tet(D)* etc. in *Salmonella* isolates. Among those genes, *tet(A)* placed within *Salmonella* genomic island (Carattoli et al. 2002), on integrons (Briggs and Fratamico 1999) and on transferable plasmids (Gebreyesm and Thakur 2005), *tet(B)* is also located on transferable plasmids (Guerra et al. 2002). These genes are simply relocated and spread between *Salmonella* isolates and generally considered important markers for identification of *Salmonella* infection (Carattoli et al. 2002). In the poultry sector, consumer opinions and demands are greatly concerned with animal welfare, food and environmental safety (Dibner and Richards 2005). So, consumer and policymakers acquire decreased use of antimicrobial growth promoters in animal feed for human health safety (Dibner and Richards 2005; Rahmani and Speer 2005).

8.2. SULFONAMIDES AND TRIMETHOPRIM

Both of these drugs are competitively inhibiting the enzymes, responsible for synthesis of tetrahydro folic acid (Alcaine et al. 2007). Sulphonamides are basically structural analogue of ρ-amino benzoic acid, involved in the synthesis of dihydrofolic acid that effectively prevent dihydrofolate synthetase in bacteria that confers the synthesis of folates (Duijkeren et al. 1994). Though sulfonamides are not effective in mammalian cells, mammalian cells directly uptake folate from food, not able to synthesize folates (Bushby 1980). While, trimethoprim inhibits dihydrofolate reductase (Mascaretti 2003). Since late 1960s, both of these drugs are bacteriostatic (Alcaine et al 2007), used in combination for bacterial infections. Sulphonamides and trimethoprim are broad spectrum antibiotics, used in the treatment of respiratory tract, alimentary tract, and urogenital tract, joint, skin and wound infections caused by Gram-positive and Gram-negative bacteria (Duijkeren et al 1994). Sulphonamides resistance among *Salmonella* isolates is due to sul gene, which is responsible for inactive dihydrofolate synthetase, instead, trimethoprim resistance ascribed to expression of dihydrofolate reductase that does not fix trimethoprim (Mascaretti 2003; Antunes et al. 2005).

8.3. BETA-LACTAMS

Carbapenems, penicillin and cephalosporins are three major sets of betalactam. Mechanisms of action of these antibiotics are facilitated by their ability to interact with penicillin binding proteins, mainly take part in the synthesis of peptidoglycan, present in bacterial cell walls. Generally, this group of medicine exhibits bactericidal activity but differs among organisms, penicillin binding proteins and beta lactams (Alcaine et al. 2007). Beta lactams move across the bacterial cell wall to approach penicillin binding proteins that are facilitated by OmpF and Omp C porins (Alcaine et al. 2007). Loss and change in porin concentrations are not considered as a way of resistance, but, decline in any one of these porin concentrations resulted in increased beta lactam resistance against cephalosporin, cefoxitin and ampicillin etc. (Alcaine et al. 2007). Beta lactams are the broad-spectrum antibiotics against Gram positive and Gram-negative bacteria. As far as *Salmonella* is concerned, bactericidal activity is observed due to inhibition of penicillin binding proteins (Angulo et al. 2000). Resistance exhibited by excretion of beta lactamases into periplasmic fluid for Gram-negative bacteria, and into the environment for the Gram-positive bacteria. Beta lactamases hydrolysed the beta lactam ring into beta amino acid, reported with no antimicrobial activity. Plasmid carries the genes for beta-lactamase production (Mascaretti 2003). Resistant *Staphylococcus aureus* has serious health issues due to Staphylococcus resistance to methicillin (Pray 2008). Later on, in the emergence of these beta lactam resistance, six-member ringed cephalosporin and five-member ringed, without sulfur carbapenems, developed. Though, these antibiotics are prescribed in treatment of acute otitis media in United States (Arrieta 2003; Cosby et al. 2015).

8.4. PHENICOLS

Chloramphenicol are the broad-spectrum antibiotics against Gram-positive and Gram-negative bacteria. Additionally, it can move across the blood brain barrier, so effective in systematic infections (Alcaine et al. 2007). But, due to widespread resistance and toxicity limited in use prescribed other than developing countries. In *Salmonella* isolates it showed resistance by two mechanisms; removal of drug through efflux pump and enzyme inactivation of O-acetyltransferase (Cannon et al. 1990). Both of these processes are reported to be effective in chloramphenicol resistance in *Salmonella* serotypes, especially in *Salmonella typhimurium* and *Salmonella agona* (Schwarz and Chaslus-Dancla 2001). Later on, florfenicol was developed and approved by FDA in 1996 for treatment of bovine respiratory pathogens but not for use in humans (White et al. 2000). Usage of florfenicol in animal farming was envisioned to reduce resistance to chloramphenicol in humans. However, chloramphenicol was excluded in Europe (1994) for animal treatment and florfenicol was permitted for veterinary use in 1995 in France (Arcangioli et al. 1999).

8.5. QUINOLONES AND FLUOROQUINOLONES

Nalidixic acid, is a synesthetic bactericidal drug, was first approved quinolone (Mascaretti 2003). These antibiotics target DNA gyrase and DNA topoisomerase IV (Wolfson and Hooper 1989), the actual mechanism is still complicated and not completely stated (Mascaretti 2003). Though, limited salmonella isolates are resistant to nalidixic and low-grade resistance to other quinolones (Molbak et al. 1999; Breuil et al. 2000). High grade resistance to quinolones is rare (Olsen et al. 2001; Casin et al. 2003). However, *Salmonella* show resistance in two ways; Target mutation to quinolone resistance determining region of gyr A, gyr B and in the par C subunit of topoisomerase IV (Cloeckaert and Chaslus Dancla 2001; Baucheron et al. 2004). Another mechanism related to alteration in the expression of AcrAB-TolC efflux system through mutations in the genes encoding system regulators that results in over-expression of the efflux system and reduce quinolone sensitivity (Baucheron et al. 2004; Oliver at al 2005). In short, not a single mutation exhibits quinolone resistance, it is the result of multiple mutations (Heisig 1993). Early fluoroquinolone was first licensed for human therapy, no resistance reported. Later, as far as licensing of fluroquinolone to animal use was authorized, rate of fluroquinolones resistant *Salmonella* in humans and animals and then in food infection vigorously increased in different countries (WHO 2011). Danofloxacin, orbifloxacin, enrofloxacin, sarafloxacin, difloxacin, and marbofloxacin were six approved fluroquinolones for animal use in United States (Martinez et al. 2006). Afterwards, enofloxacin and sarafloxacin, authorized for treatment of respiratory diseases in poultry, have been excluded from approved list, because of amplified antibiotic resistance to Campylobacter and *Salmonella* spp. improved in human illness (Nelson et al. 2007).

9. CHICKEN- MEAT OR EGG ARE THE CARRIERS OF SALMONELLOSIS TO HUMANS

Salmonella contaminated animal-based products induce 3% worldwide food borne diseases with approximately 80 million infections (El-Saadony et al. 2022). Salmonellosis is the disease condition associated with pathogenic bacteria *Salmonella*, causing severe damage to the poultry sector all over the world. Though, it is a zoonotic bacterium which can be transferred from animals to humans. The transmission can occur by following different ways.

- An infected animal direct contact
- By consuming or handling contaminated animal products like raw meat or eggs from turkey and chicken
- Interaction with contaminated equipment or with infected vectors such as pets or insects.

However, raw chicken products or frozen chicken meat and also eggs of backyard hens are the amplest cause of animal facilitated *Salmonella* infections in humans.

Infective dose of salmonellosis for humans ranges from 10^4 to 10^6 cells or more, or it could be low as 10^1 to 10^2 cells in a low immunity person, or, a human consumes contaminated high fat matrix food like cheese, chocolates, peanut butter, pizza etc. However, *Salmonella enterica* is a documented serovar of *Salmonella*, causing infection in humans based on raw poultry and poultry meat products, well known for economic and public health implications. It's a zoonotic pathogen that can readily pass from animals to humans, while consuming contaminated meat, animal-based products or other food products contaminated with animal fecal material. The infection spread either through direct or in direct contact with colonized birds or by consuming contaminated water (Lammerding 2006; Chai and Mohan 2011). The main niche of *Salmonella* species is the gastrointestinal tract of humans and farm animals, reptiles, birds, fish, amphibians and shellfish (Heinitz et al. 2000; Bailey et al. 2010; Machado et al. 2020). No doubt, fecal contamination is the major source of water and food contamination plays a key role in the spread of salmonellae in the environment and ultimately, the food supply chain. In such a way, meat animals became infected and became a carrier or reservoir of salmonellae.

10. EFFECT OF SALMONELLOSIS ON HUMAN HEALTH

Salmonellosis is one of the most common foodborne infections. The genus Salmonella comprises 2600 serovars, among them, more than 100 because of a cause of infection in humans (CDC 2020). In humans, salmonellosis was exhibited by typhoid fever. Common signs and symptoms of typhoid fever includes high fever, cough, malaise and headache (Fig. 1).

Among humans, the most common serovar is *Salmonella enteritis*, causing typhoid fever or enteric fever. *Salmonella* is motile Enterobacteriaceae that produce variety of GIT infections ranging from simple fever diffuse abdominal pain, and constipation however, untreated typhoid leads to intestinal hemorrhage, delirium, bowel perforation, obtundation and death within 1 month of progression of disease (Christie 1987; Butt et al. 2022). Patients may also suffer with short-term or long-term neuropsychiatric issues. Typhoid is derived from ancient Greek word means, cloud, indicating the prolonged severity of the disease related to long-lasting neuropsychiatric effects among the untreated. About 21 million people in the year suffer from typhoid fever in the World. With time, it has developed resistance to antibiotics. In the year 2016, Multi Drug Resistance (MDR) was reported in Pakistan. Though, only three classes of antibiotics, carbapenems, tigecycline and azithromycin are effective against *Salmonella* serovars (Butt et al. 2022).

Salmonella enters the GIT through phagocytic cells, which then present to macrophages of lamina propria. Macrophages recognize pathogen associated molecular patterns (PAMPS) such as lipopolysaccharides and flagella through their toll like receptor TLR-4, TLR-5/CD-14/ MD2 complexes. In this way, intestinal cells and macrophages mobilize neutrophils and T-cells with interlekin-8. At this stage, inflammation is quiet enough to suppress the infection (Parry et al. 2002; Raffatellu et al. 2006). By distal ileum, *S. typhi* and *paratyphi* enter the host system with the help of specialized fimbriae that support to adhere to the epithelium over clusters of lymphoid tissue in the ileum, commonly known as Peyer Patches, main entrance for macrophages to enter into lymphoid system from Gut. Once bacterium enters, induce host macrophages to attract more macrophages (Raffatellu et al. 2006). Additionally, these serotypes are able to produce Quorum sensing, intracellular communication through organism coordinate swarming and produce biofilm (Rana et al. 2021).

Later, typhoid introducing *Salmonella* adopt macrophages cellular machinery for their reproduction (Ramsden et al. 2007), by mesenteric lymph nodes to thoracic duct, lymphatics that leads to reticuloendothelial tissues of the spleen, liver, lymph nodes and bone marrow. As they approach, and establish a favorable environment, they start to flourish by continuing multiplications. This way, they allow *Salmonella* to enter into the bloodstream (Parry et al. 2002).

Though, bacterium infect gallbladder either *via* bacteremia or direct extension of infected bile, reverse back to GIT in the bile and again infect Peyer Patches. However, bacteria were not able to infect the host shed in the stool and became a carrier to infect others (Christie 1987; Parry et al. 2002). So, bacterium shed by a single carrier may have numerous genotypes, quite hard to follow an outbreak of its origin (Chiou et al. 2013).

Typhoid causing *Salmonella*, generally have non-human vectors, even though an inoculum as small as 100,000 germs of typhi able to infect 50% of healthy person (Levine et al. 2001). Besides this, Paratyphi requires much higher volume to infect, less pervasive in rural areas, easily transmitted through street foods and provides a micro-friendly environment to bacterium. In short, their route of transmission is slightly different from one another, for typhoidal *Salmonella* generally modes of transmission are;

- Oral transmission through contaminated water
- Oral transmission *via* food/ beverages handles by infected person
- Hand-to-mouth transmission after using unhygienic commode and wash basin (Earampamoorthy et al. 1975; Ali et al. 2006; Ram et al. 2007)

Typhoidal *Salmonella* have the ability to survive in the low pH (Fig. 2), as much as 1.5. Medicines and procedures like antacids, H2 blockers gastrectomy, proton-pump inhibitors and achlorhydria reduce stomach acidity, which helps to induce *S. typhi* infection (Parry et al. 2002).

11. METHODS TO PREVENT *SALMONELLA* OUTBREAK

Poultry signifies a natural habitat for *Salmonella* and Campylobacter. Though, twice of them are commonly found in GI tract of and considered as commensal bacterium. Best exercise to control *Salmonella* is in live poultry production. So, the best strategic plan for Salmonella control is anticipation in birds based on three main facts:

- By following effective hygiene measures for the prevention of incidence of *Salmonella* into the farm/flock
- By controlling the spread of pathogens with in the farm/flock
- By accompanying prophylactic procedures to recover immune resistance of animals against pathogenic bacterium

To follow these key steps, need to manage or organize short footnotes;

11.1. PROVIDE HEALTHY ENVIRONMENT

Dead animals and Broken eggs (potential source of infection) should be immediately cleared. Troughs must be clean from dropping. Poultry house should be fumigated before restocking. Clean water and feed are very much essential; feed should be stored, kept dry and protected from rodents and pets, while drinking water flow rate should be sufficient to offer the birds with adequate amounts of water, but not too much that the floor becomes wet.

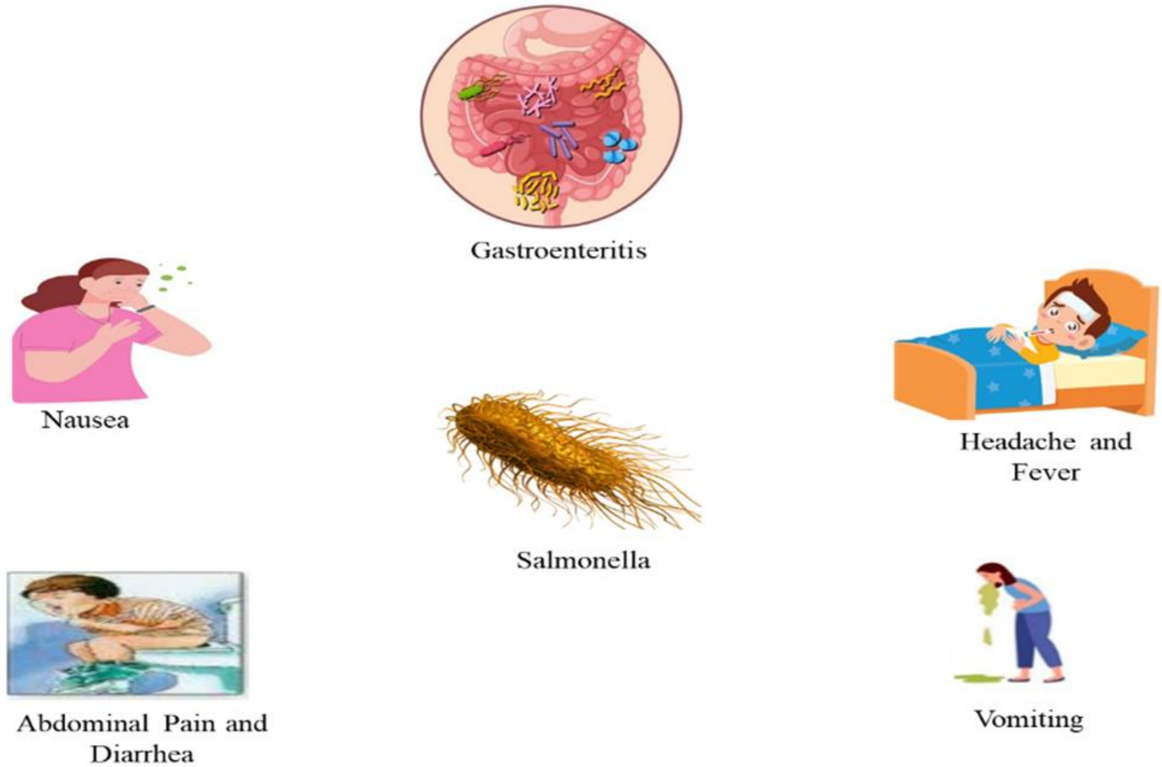

Fig. 1: Clinical manifestation of Human Salmonellosis.

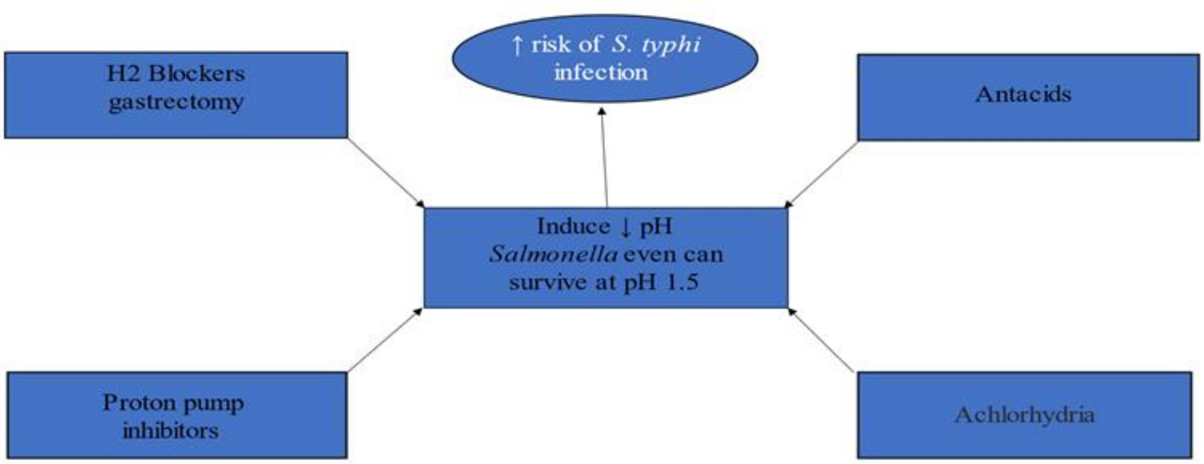

Fig. 2: Typhoidal Salmonella survival in reduce stomach activity.

11.2. LITTER SHOULD BE DRY

Used litter should be removed regularly after specific time material. Well absorptive material such as straw granulates and wood shaving for litter recommended. Adequate water supply granted; excess water supply wet the litter. Birds must be monitored for diarrhea to avoid wet droppings.

11.3. MINIMIZE THE CONTACT

Only a few people were allowed to visit the flock in order to reduce the spread of *Salmonella*. Instruments and wear clothes should be entirely used for the poultry house (Heinzl, 2022) Other than this strategic plan, there are various approaches used to avoid the incidence of Salmonellosis in poultry such as;

11.3.1. CHITOSAN

Chitosan is a polysaccharide, with diverse medical application present in the hard outer skeleton of lobsters, shrimp and shellfish (Attia et al. 2022). Chitosan molecules cause metal ion chelation and vital nutrients of bacteria decrease bacterial growth (Rabea et al. 2003). *In vitro* studies reported that chitosan exhibit antibacterial activity against *S. aureus* and *S. paratyphi* (Islam et al. 2011). Chitosan is the hard sugar-induced host immune modulating response against pathogens (Lee et al. 2009).

11.3.2. NANOPARTICLES

Nanomaterials seek more attention in this era due to their exceptional physical and chemical characteristics (Yousry et al. 2020; Reda et al. 2021; Salem et al. 2021). Zinc oxide nanoparticles (3mg/g) along with poultry ration found effective against *S. typhimurium* and *S. aureus* (De Silva et al. 2021). Similarly, incorporation of gold nanoparticles exhibited antibacterial activity against *S. typhimurium* (Reda et al. 2021). Silver nanoparticles along with rosemary extract revealed antibacterial effects against *E. coli, S. enteritidis* and *S. typhimurium* (Mohamed et al. 2017).

11.3.3. PHYTOCHEMICALS

Plants produce phytochemicals as secondary metabolites to protect themselves from bacteria, yeast, and mold infection. Extraction and purification of such phytogenic substances, found effective against *Salmonella* in poultry. Each phytochemical has its own mode of action, due to diverse phytochemical nature and mechanism of such phytogenic substance, considered as no resistance develop, but lately *S. aureus*, *E. coli*, *E. faecalism,* and *S. typhimurium* showed resistance to sum components of herbal drugs (Khan et al. 2009). Phytochemicals are hydrophobic in nature, *Salmonella*- Gram negative bacteria are less susceptible to such phytochemicals, because only hydrophilic solutes can pass through the bacterial cell wall. Though, invasion inside the cell could be enhanced by mixing phytochemicals with an emulsifier, but efficacy depends upon the chemical composition of these phytochemicals (Heinzl 2022).

11.3.4. ESSENTIAL OILS

Essential oils are the volatile, aromatic, and oily compounds extracted from different parts of the plant (Abd El-Hack et al. 2022). Such beneficial oils are potent digestive stimulants, hypolipemic agents, immunostimulants, antifungal, antibacterial growth promoter subtances that generate positive effects on egg production and broiler performance (Nahed et al. 2022). *Cymbopogon citratus* (lemon grass) oil extract showed antibacterial activity against *S. enterica* and *S. typhimurium* (Alagawany et al. 2021). Similarly, eugenol, carvacrol, trans-cinnamaldehyde and thymol have effective antibacterial effects against *Salmonella* and Campylobacter in layer and broiler chicken (Johny et al. 2010).

11.3.5. PREBIOTICS AND PROBIOTICS

Prebiotics are not easily digestible substances consumed by valuable microbiota in the intestine (Yaqoob et al. 2021). Fructooligosaccharide incorporation in poultry ration as prebiotic improves growth performance, enlarges small intestinal villi length and enhances bacterial colonization in broilers (Xu et al. 2003). Addition of fructooligosaccharide increases the production of short chain fatty acids that alters gut microbiota towards beneficial bacteria that is causative to growth of pathogenic *Salmonella* and improves innate and immunological responses in broiler chicken (Shang et al. 2015).

Probiotics are the living microorganisms that help in development and growth of the host when administered in suitable concentrations (Mack 2005). Such beneficial bacteria generate bactericidal and bacteriostatic chemicals in the intestine which are toxic to pathogens, such as, in *vitro* studies revealed that Lactobacillus spp. ferment saccharides and produce lactic acid that lowers intestinal pH and inhibits pathogenic bacterial growth like *S. typhimurium* and *E. coli* (Abd El-Hack et al. 2021). This phenomenon is approved in *in vivo* studies, as subset of fatty acids (SCFs) like acetate propionate and butyrate amplified, occurrence of *E. coli* and *Salmonella enterica* reduced in broiler cecum (Van Der Wielen et al. 2000).

In the start of 20th century, the life style is quiet change, life is too busy and hectic schedule tend people to eat outdoor cooked food from restaurants and hotels. Most potently, in developing countries, the food hygiene is compromised, in such a way, these restaurants and hotels are common places for the onset of an outbreak (Spackova et al. 2019). By adopting hygiene conditions, proper cleaning of dishes and washing hands of the employees, storage of food in an appropriate manner and cooking food at adequate temperature can reduce the risk of Salmonellosis (Ibram et al. 2007; Appling et al. 2018). So, poultry and meat farmers need to maintain food security. Though, prevalence of *Salmonella* and virulence of strain is equally important. Eggs are also another source of *Salmonella* infection. Although, different methods are implemented these days for decontamination of eggs like freeze drying, pasteurization, hot air and microwave heating (Oscar 2020; Keerthirathne et al. 2017). But with these techniques the properties of eggs may be affected. For immune compromised individuals or for vulnerable patients microbiologically decontaminated eggs are recommended. Drinking water is also an important source for the spread of infection. Proper storage and supply of clean filtered water to the public is the necessary step, should be taken by the Government and authorities to avoid the risk of Salmonellosis. Besides this, demanding hygiene practices required to be implanted in the food preparation and processing industry, around the environmental controls in ready to cook and convenient food production.

12. CONCLUSION

In conclusion, zoonosis *Salmonella* engenders high cost in the poultry sector. With increasing population and inflation rate, protein demands are mainly focused on the poultry industry. As Salmonellosis is transferred from animal to human *via the food* chain, it needs to be controlled by all means. Antibiotics are the drugs to combat such pathogens but emerging MDR strains of *Salmonella* are still a potential risk to public health locally and beyond. In this way, implementation of more rigorous preventive and control measures is necessary, because surveillance has major concern and impact. Along these antibiotics, poultry producers need to seek, active but not, resistance generating natural solutions or feed additives against *Salmonella* for further development.

REFERENCES

Abd El Ghany M et al., 2017. Enteric infections circulating during Hajj seasons, 201-2013. Emerging Infectious Diseases 23: 1640.

Abd El-Hack ME et al., 2022. Essential oils and their nano emulsions as green alternatives to antibiotics in poultry nutrition: a comprehensive review. Poultry Science 101(2): 101584.

Abd El-Hack ME et al., 2021. Prebiotics can restrict *Salmonella* populations in poultry: a review. Animal Biotechnology 33(7): 1668-1677.

Abebe E et al., 2020. Review on major food-borne zoonotic bacterial pathogens. Journal of Tropical Medicine :4674235.

Ahmad S et al., 2021. A skeleton in the closet: the implications of COVID-19 on XDR strain of typhoid in Pakistan. Public Health in Practice 2: 100084.

Akinyemi KO et al., 2021. A systemic review of literatures on human *Salmonella enterica* serovars in Nigeria (1999-2018). Journal of Infections in Developing Countries 15(9): 1222-1235.

Alagawany M et al., 2021. Use of lemongrass essential oil as a feed additive in quail's nutrition: its effect on growth, carcass, blood biochemistry, antioxidant and immunological indices, digestive enzymes and intestinal microbiota. Poultry Science 100(6): 101172.

Alcaine SD et al., 2007. Antimicrobial resistance in Non-Typhoidal *Salmonella*. Journal of Food Protection 70: 780–790.

Ali S et al., 2006. PARK2/PACRG polymorphisms and susceptibility to typhoid and paratyphoid fever. Clinical and Experimental Immunology 144(3): 425-31.

Al-Rifai RH et al., 2019. Prevalence of enteric non-typhoidal Salmonella in humans in the Middle East and North Africa: A systematic review and meta-analysis. Zoonoses Public Health 66: 701-728.

Andrews-Polymenis HL et al., 2010. Salmonella biology, pathogenesis, and prevention. Infection and Immunity 78: 2356-2369.

Angulo FJ et al., 2000. Origins and consequences of antimicrobial-resistant nontyphoidal Salmonella: Implications for use of flouroquinolones in food animals. Microbial Drug Resistance 6: 77–83.

Antunes P et al., 2005. Dissemination of sulfonamide resistance genes (sul1, sul2, and sul3) in Portuguese Salmonella enterica strains and relation with integrons. Antimicrobial Agents and Chemotherapy 49: 836–839.

Appling XS et al., 2018. Understanding the relation between establishment food safety management and risk factor violations cited during routine inspections. Journal of Food Protection 81: 1936-40.

Arcangioli MA et al., 1999. A new chloramphenicol and florfenicol resistance gene flanked by two integron structures in *Salmonella Typhimurium* DT104. FEMS Microbiology Letters 174: 327–332

Arrieta A, 2003. High dose azithromycin versus high dose amoxicillin-clavulanate for treatment of children with recurrent or persistent acute otitis media. Antimicrobial Agents and Chemotherapy 47: 3179–3186.

Attia MM et al., 2022. Evaluation of the antiparasitic activity of the chitosan-silver nanocomposites in the treatment of experimentally infested pigeons with *Pseudolynchia canariensis*. Saudi Journal of Biological Sciences *29*(3): 1644-1652.

Bailey JS et al., 2010. Salmonella. Pages 108–118 in Pathogens and Toxins in Food: Challenges and Interventions. VK Juneja and JN Sofos, eds. ASM, Washington, D.C.

Baucheron S et al., 2004. Role of TolC and parC in -high-level fluorquinolone resistance in Salmonella enterica serotype Typhimurium phage type DT204. Journal of Antimicrobial Chemotherapy 53: 657–659.

Beachey ED, 1981. Bacterial Adherence: Adhesin-Receptor Interactions Mediating the Attachment of Bacteria to Mucosal Surfaces. The Journal of Infectious Diseases 143(3): 325–345.

Binter C et al., 2011. Transmission and control of salmonella in the pig feed chain: a conceptual model. International Journal of Food Microbiology 145: S7–17.
Borsoi A et al., 2011. Behavior of *Salmonella Heidelberg* and *Salmonella Enteritidis* strains following broiler chick inoculation: evaluation of cecal morphometry, liver and cecum bacterial counts and fecal excretion patterns. Brazilian Journal of Microbiology 42: 266-273.
Brenner FW et al., 2000. *Salmonella* nomenclature. Journal of Clinical Microbiology 38: 2465-7.
Breuil J et al., 2000. Antibiotic resistance in salmonellae isolated from humans and animals in France: Comparative data from 1994 and 1997. Journal of Antimicrobial Chemotherapy 46: 965–971.
Briggs EC and Fratamico PM, 1999. Molecular characterization of an antibiotic resistance gene cluster of Salmonella Typhimurium DT104. Antimicrobial Agents and Chemotherapy 43: 846–849.
Bryan FL et al., 197. *Salmonella* infections. In: Food-borne infections and intoxications. (Eds. Reimann H. & Bryan, F.L.). New York, USA. Academic Press 73-130.
Bushby SRM, 1980. Sulfonamide and trimethoprim combinations. Journal of American Veterinary and Medical Association 176: 1049–1053.
Butaye P et al., 2006. The clonal spread of non-typhi Salmonella serotypes. Microbes and Infection 8: 1891– 1897.
Butt M et al., 2022. Rising XDR-typhoid fever cases in Pakistan: are we heading back to the pre-antibiotic era? Frontiers in Public Health 9: 794868.
Cannon M et al., 1990. A comparative study on the inhibitory actions of chloramphenicol, thiamphenicol and some fluorinated derivatives. Journal of Antimicrobial Chemotherapy 26: 307–317
Carattoli A et al., 2002. Antibiotic resistance genes and Salmonella genomic island 1 in Salmonella enterica serovar Typhimurium isolated in Italy. Antimicrobial Agents and Chemotherapy 46: 2821–2828.
Carattoli A, 2003. Plasmid-mediated antimicrobial resistance in Salmonella enterica. Current Issues in Molecular Biology 5: 113–122.
Carter GR and Wise DJ 2004.*"Essentials of Veterinary Bacteriology & Mycology*". 6th ed., Blackwell publishing Company. Iowa State Press, USA 137-140.
Casin I et al., 2003. Fluoroquinolone resistance linked to GyrA, GyrB, and ParC in mutations in *Salmonella enterica Typhimurium* isolates in humans. Emerging Infectious Diseases 9:1455–457.
Castanon JIR, 2007. History of the use of antibiotic as growth promoters in European poultry feeds. Poultry Science 86: 2466–2471.
Center for Disease Control and Prevention (CDC), 2013a. Multistate Outbreak of Human Salmonella Infections Linked to Live Poultry.
Center for Disease Control and Prevention (CDC), 2013b. Multistate Outbreak of Human Salmonella Typhimurium Infections Linked to Live Poultry in Backyard Flocks.
Center for Disease Control and Prevention (CDC), 2020. Serotypes and the Importance of Serotyping Salmonella. Centers for Disease Control and Prevention February 21, 2020.
Chai SJ and Mahon B, 2011. Memorandum to record: Foodborne illness from Salmonella and Campylobacter associated with poultry. United States Department of Health and Human Services, Washington, D.C.
Chiou CS et al., 2013. Salmonella enterica serovar Typhi variants in long-term carriers. Journal of Clinical Microbiology 51(2): 669-72.
Chirico C et al., 2020. The first Italian case of XDR Salmonella Typhi in a traveler returning from Pakistan, 2019: an alert for increased surveillance also in European countries? Travel Medicine and Infectious Diseases 36: 101610.
Chopra I and Roberts M, 2001. Tetracycline antibiotics: Mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiology and Molecular Biology Reviews 65: 232–260.
Christie AB, 1987. *Infectious Diseases: Epidemiology and Clinical Practice*. 4th ed. Edinburgh, Scotland: Churchill Livingstone.
Cloeckaert A and Chaslus-Dancla E, 2001. Mechanisms of quinolone resistance in Salmonella. Veterinary Research 32: 291–230.
Cosby DE et al., 2015. Salmonella and antimicrobial resistance in broilers: A review. Journal of Applied Poultry Research 24(3): 408-426.
Croft AC et al., 2007. Update on the antibacterial resistance crisis. Medical Science Monitor 13: RA103–RA118.

Crump JA et al., 2011. Antimicrobial resistance among invasive nontyphoidal *Salmonella enterica* isolates in the United States: national antimicrobial resistance monitoring system, 1996 to 2007. Antimicrobial Agents and Chemotherapy 55: 1148-1154.

Diarra MS et al., 2007. Impact of feed supplementation with antimicrobial agents on growth performance of broiler chickens, Clostridium perfringens and Enterococcus counts, and antibiotic resistance determinants in Escherichia coli isolates. Applied Environmental Microbiology. 73:6566– 6576.

Dibner and Richards. 2005. Antibiotic growth promoters in agriculture: history and mode of action. Poultry Science. 84:634–643.

De Reu K et al., 2006. Eggshell factors influencing eggshell penetration and whole egg contamination by different bacteria, including Salmonella enteritidis. International journal of Food Microbiology 112(3): 253-260.

De Silva C et al., 2021. The mechanistic action of biosynthesised silver nanoparticles and its application in aquaculture and livestock industries. Animals 11(7): 2097.

Dieye Y et al., 2009. The Salmonella pathogenicity island (SPI) 1 contributes more than SPI2 to the colonization of the chicken by *Salmonella enterica* serovar *Typhimurium*. BMC Microbiology 9: 3–16.

Dione MM et al., 2011. Clonal differences between non-typhoidal Salmonella (NTS) recovered from children and animals living in close contact in The Gambia. PLoS Neglected Tropical Diseases. 5, e1148.

Duijkeren E et al., 1994. Trimethoprim/sulfonamide combinations in the horse: A review. Journal of Veterinary Pharmacology and Therapy 17: 64–73.

Dunkley CS et al., 2008. Growth and genetic responses of Salmonella Typhimurium to pH-shifts in an anaerobic continuous culture. Anaerobe 14: 35–42.

Earampamoorthy S and Koff RS, 1975. Health hazards of bivalve-mollusk ingestion. Annals of Internal Medicine 83(1): 107-10.

EFSA 2021. The European Union one health 2019 zoonosis report. EFSA Journal 19: 06406.

El-Saadony MT et al., 2022. The control of poultry salmonellosis using organic agents: an updated overview. Poultry Science 101: 101716.

El-Sharkawy H, 2017. Epidemiological, molecular characterization and antibiotic resistance of *Salmonella enterica* serovars isolated from chicken farms in Egypt. Gut Pathogens 9: 8.

Euzeby JP, 1999. Revised Salmonella nomenclature: designation of Salmonella enterica (ex-Kauffmann and Edwards 1952) Le Minor and Popoff 1987 sp. nom., nom. rev. as the neotype species of the genus Salmonella Lignieres 1900 (approved lists 1980), rejection of the name *Salmonella choleraesuis* (Smith 1894) Weldin 1927 (approved lists 1980), and conservation of the name *Salmonella typhi* (Schroeter 1886) Warren and Scott 1930 (approved lists 1980). Request for an opinion. International Journal of Systematic Bacteriology 49: 927-930.

European Centre for Disease Prevention and Control (ECDC). 2015. The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2014. EFSA Journal 13: 4329.

Fairley C, 2007. From Pasteur to Pathogenomics: A brief history of infectious disease and the efforts to fight it. Electronic Working Papers Series. W. Maurice Young Centre for Applied Ethics. Accessed Oct 2011. University of British Columbia.

Fardsanei F et al., 2018. Antimicrobial resistance, virulence genes and genetic relatedness of *Salmonella enterica* serotype *enteritidis* isolates recovered from human gastroenteritis in Tehran, Iran. Journal of Global Antimicrobial Resistance 12: 220-226.

Fasina YO, 2010. Influence of Salmonella enterica Serovar Typhimurium Infection on Intestinal Goblet Cells and Villous Morphology in Broiler Chicks. Avian Diseases 54(2): 841-847.

Fatima MM et al., 2021. Morbidity and mortality associated with typhoid fever among hospitalized patients in Hyderabad District, Pakistan, 2017–2018: retrospective record review. JMIR Public Health and Surveillance 7(5): e27268.

Feasey NA et al., 2015.Three epidemics of invasive multidrug-resistant Salmonella bloodstream infection in Blantyre, Malawi, 1998–2014. Clinical Infectious Disease 1(4): 363-371.

Fluit AC, 2005. Towards more virulent and antibiotic-resistant Salmonella? FEMS Medical Microbiology and Immunology 43: 1–11.

Foley SL and Lynne AM, 2008. Food animalassociated Salmonella challenges: Pathogenicity and antimicrobial resistance. Journal of Animal Science 86: E173–E187.

Ford L et al., 2016. Increasing incidence of Salmonella in Australia, 2000-2013. PLoS ONE 11:e0163989.

Fu P et al., 2019. Analysis of foodborne disease outbreaks in China mainland in 2015. Chinese Journal of Food Hygiene 33: 64-70.

Gebreyesm WA and Thakur S, 2005. Multidrugresistant *Salmonella enterica* serovar Muenchen from pigs and humans and potential interserovar transfer of antimicrobial resistance. Antimicrobial Agents and Chemotherapy 49: 503–511.

Gille-Johnson P et al., 2000. *Salmonella* Virchow meningitis in an adult. Scandinavian Journal of Infectious Diseases 32(4): 431-433.

Godbole GS et al., 2018. First report of CTX-M-15 Salmonella Typhi from England. Clinical Infectious Diseases 66 (12): 1976-1977.

Gopee NV et al., 2000. Retrospective and longitudinal study of salmonellosis in captive wildlife in Trinidad. Journal of Wildlife Diseases 36(2): 284 -293.

Guerra B et al., 2002. Characterization of a self-transferable plasmid from Salmonella enterica serotype Typhimurium clinical isolates carrying two integron-borne gene cassettes together with virulence and drug resistance genes. Antimicrobial Agents and Chemotherapy 46: 2977–2981.

Gut AM et al., 2018. *Salmonella* infection - prevention and treatment by antibiotics and probiotic yeasts: a review. Microbiology 164: 1327-44.

He Y et al., 2023. Epidemiology of foodborne diseases caused by Salmonella in Zhejiang Province, China, between 2010 and 2021. Frontiers in Public Health 11: 1127925.

Heinitz ML et al., 2000. Incidence of Salmonella in fish and seafood. Journal of Food Protection 63: 579–592.

Heinzl I, 2022. Salmonella in poultry: What are the most effective natural solutions?.

Heisig P, 1993. High-level fluoroquinolone resistance in a *Salmonella Typhimurium* isolates due to alterations in both gyrA and gyrB genes. Journal of Antimicrobial Chemotherapy 32: 367–377

Heredia N and García S 2018. Animals as sources of food-borne pathogens: A review. Animal Nutrition, 4(3): 250 - 255.

Hidalgo-Vila J et al., 2007: *Salmonella* in free-living terrestrial and aquatic turtles. Veterinary Microbiology 119: 311-315.

Hill AA et al., 2016. A farm transmission model for salmonella in pigs, applicable to E.U. member states. Risk Analysis 36: 461–81.

Hugas M and Beloeil PA, 2014. Controlling salmonella along the food chain in the European union - progress over the last ten years. Eurosurveillance 19: 20804.

Ibram S et al., 2007. An outbreak of gastroenteritis in a campsite in Romania, July 2007. Euro Surveillance 12: E070816.

Islam MM et al., 2011. In vitro antibacterial activity of shrimp chitosan against Salmonella paratyphi and Staphylococcus aureus. Journal of Bangladesh Chemical Society 24(2): 185-90.

Johny AK et al., 2010. Antibacterial effect of trans-cinnamaldehyde, eugenol, carvacrol, and thymol on Salmonella Enteritidis and Campylobacter jejuni in chicken cecal contents in vitro. Journal of Applied Poultry Research *19*(3): 237-244.

Jones FT and Ricke SC, 2003. Observations on the history of the development of antimicrobials and their use in poultry feeds. Poultry Science 82: 613–617.

Jordain FT and Pattison M, 1996. *"Poultry Disease*". 4th ed., W.B. Saunders Company Ltd., London, pp. 1-4.

Keerthirathne TP et al., 2017. Reducing risk of salmonellosis through egg decontamination processes. International Journal of Environmental Research and Public Health 14: 335.

Khan R et al., 2009. Antimicrobial activity of five herbal extracts against multi drug resistant (MDR) strains of bacteria and fungus of clinical origin. Molecules 14(2): 586-597.

Kim C et al., 2021. The molecular basis of extensively drug-resistant Salmonella Typhi isolates from pediatric septicemia patients. PLoS One 16 (9): e0257744.

Klemm EJ et al., 2018. Emergence of an extensively drug-resistant *Salmonella enterica* serovar Typhi clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third-generation cephalosporins. MBio 9(1): e00105-00118.

Kloska F et al., 2017. Implementation of a risk-orientated hygiene analysis for the control of salmonella JAVA in the broiler production. Current Microbiology 74: 356–64.

Koonse B et al., 2005. *Salmonella* and the sanitary quality of aquacultured shrimp. Journal Food Prot, 68(12): 2527-2532.

Kuang X, 2015. Serotypes and antimicrobial susceptibility of Salmonella spp. isolated from farm animals in China. Frontiers in Microbiology 6 (2015): 602.

Kuehn B, 2019. Antibiotic resistance threat grows. JAMA, 322, 2376.

Lake R et al., 2002.*"Risk profile: Salmonella (nontyphoid) in poultry (whole & pieces)*". Institute of Environmental Science & Research Limited, Christchurch Science Center Newzealand, A crown Research Institute.

Lammerding AM, 2006. Modeling and risk assessment for Salmonella in meat and poultry. Journal AOAC International 89: 543–552.

Lecis R et al., 2011. Detection and characterization of *Mycoplasma* spp. and *Salmonella* spp. in free-living European tortoises (*Testudo hermanni*, *Testudo graeca, Testudo marginata*). Journal of Wildlife Diseases 47(3): 717-724.

Lee BC et al., 2009. In vitro and in vivo antimicrobial activity of water-soluble chitosan oligosaccharides against *Vibrio vulnificus*. International Journal of Molecular Medicine *24*(3): 327-333.

Lertworapreecha M et al., 2013: Antimicrobial resistance of Salmonella enterica isolated from pork, chicken and vegetables in southern Thailand. Jundishapur Journal of Microbiology 6: 36-41.

Levine MM et al., 2001. Host-Salmonella interaction: human trials. Microbes and Infect*ion* 3(14-15):1271-9.

Machado Junior PC et al., 2020. Modeling *Salmonella* spread in broiler production: Identifying determinants and control strategies. Frontiers in Veterinary Science 7: 564.

Mack DR, 2005. Probiotics: mixed messages. Canadian Family Physician 51(11): 1455.

Majowicz SE et al., 2010. International Collaboration on Enteric Disease "Burden of Illness", S. The global burden of nontyphoidal Salmonella gastroenteritis. Clinical Infections 50: 882-889.

Martinez M et al., 2006. Pharmacology of the fluoroquinolones: A perspective for the use in domestic animals. Veterinary Journal 172:10–28.

Mascaretti OA, 2003. Bacteria versus Antimicrobial Agents: An Integrated Approach. ASM, Washington, D.C.

Matulova M et al., 2013. Chicken innate immune response to oral infection with Salmonella enterica serovar *Enteritidis*. Veterinary Research 44(1): 1-11.

Mbae C et al., 2020. Factors associated with occurrence of salmonellosis among children living in Mukuru slum, an urban informal settlement in Kenya. BMC Infectious Diseases 20: 422.

Meiring JE et al., 2021. Burden of enteric fever at three urban sites in Africa and Asia: A multicentre population-based study. Lancet Global Health 9: e1688-e1696.

Merchant IA and Packer RA, 1977. *"Veterinary Bacteriology & Virology".* 7th ed., Iowa State University Press, Ames, Iowa, USA 286-290.

Mohamed M et al., 2017. Enhancement of antimicrobial sensitivity of Salmonella and *Escherichia coli* strains isolated from chickens using silver nanoparticles in Assiut governorate. Zagazig Veterinary Journal 45(3): 273-282.

Molbak K et al., 1999. An outbreak of multidrug-resistant *Salmonella enterica* serotype *Typhimurium* DT104. New England Journal of Medicine 341:1420–1425.

Munyaka PM et al., 2012. Local and systemic innate immunity in broiler chickens supplemented with yeast-derived carbohydrates. Poultry Science 91(9): 2164-2172.

Myruvik QN et al., 1976.*"Salmonella In: Fundamental of Medical Bacteriology & Mycology*". Chapter 18, Henry Kimpton Publisher, London, pp. 245-247.

N'cho HS, 2019. Notes from the field: Typhoid fever outbreak—Harare, Zimbabwe, October 2017–February 2018. MMWR Morbidity and Mortality Weekly Report 68:44-45.

Nahed A et al., 2022. Phytochemical control of poultry coccidiosis: a review. Poultry Science 101(1): 101542.

Namata H et al., 2008. Salmonella in belgian laying hens: an identification of risk factors. Preventive Veterinary Medicine 83:323–36.

Namata H et al., 2009. Identification of risk factors for the prevalence and persistence of salmonella in belgian broiler chicken flocks. Preventive Veterinary Medicine 90:211–22.

Nelson JM et al., 2007. Fluoroquinolone-resistant Campylobacter species with the withdrawal of fluoroquinolones from use in poultry: A public health success story. Clinical Infectious Diseases 44:977–980.

Ngogo FA et al., 2020. Factors associated with Salmonella infection in patients with gastrointestinal complaints seeking health care at regional hospital in Southern Highland of Tanzania. BMC Infectious Diseases 20:135.

Nielsen LR and Nielsen SS, 2012. A structured approach to control of salmonella dublin in 10 danish dairy herds based on risk scoring and test-and-manage procedures. Food Research International. 45:1158–65.

Nizamuddin S et al., 2021. Continued outbreak of ceftriaxone-resistant *Salmonella enterica* serotype *typhi* across Pakistan and assessment of knowledge and practices among healthcare workers. American Journal of Tropical Medicine and Hygiene 104 (4):1265-1270.

Oliver AM et al., 2005. Over expression of the multidrug efflux operon acrEF by insertional activation of IS1 or IS10 elements in *Salmonella enterica* serovar *Typhimurium* DT204 acrB mutants selected with fluoroquinolones. Antimicrobial Agents and Chemotherapy 49:289–301.

Olsen SJ et al., 2001. A nosocomial outbreak of fluoroquinolone-resistant Salmonella infection. New England Journal of Medicine 344:1572–1579.

Oludairo O et al., 2022. Review of Salmonella Characteristics, History, Taxonomy, Nomenclature, Non Typhoidal Salmonellosis (NTS) and Typhoidal Salmonellosis (TS). Zagazig Veterinary Journal 50:160-171.

Oscar T, 2020. Salmonella prevalence alone is not a good indicator of poultry food safety. Risk Analysis 41:110-30.

Padungtod P and Kaneene JB, 2006. *Salmonella* in food animals and humans in northern Thailand. International Journal of Food Microbiology 108: 346 -54.

Painter J et al., 2013. Attribution of foodborne illnesses, hospitalizations, and deaths to food commodities by using outbreak data, United States, 1998–2008. Emerging Infectious Diseases 19:407–15.

Parry CM et al., 2002. Typhoid fever. New England Journal of Medicine 28. 347(22):1770-82.

Percipalle M et al., 2011. *Salmonella* infection in illegally imported spur-thighed tortoises (Testudo graeca). Zoonoses and Public Health 58: 262-269.

Pires SM et al., 2014. Source attribution of human salmonellosis: an overview of methods and estimates. Foodborne Pathogen Diseases 11:667-76.

Pray L, 2008. Antibiotic resistance, mutation rates and MRSA. National Journal of Education 1:1–2

Rabea EI et al., 2003. Chitosan as antimicrobial agent: applications and mode of action. Biomacromolecules 4(6): 1457-1465.

Raffatellu M et al., 2006. Capsule-mediated immune evasion: a new hypothesis explaining aspects of typhoid fever pathogenesis. Infect Immun*ology* 74(1):19-27.

Rahman HS and Othman HH, 2017. *"Salmonella Infection: The common cause of human food poisoning".* Progress in Bioscience and Bioengineering 1(1):5-10.

Rahmani HR and Speer W, 2005. Natural additives influence the performance and humoral immunity of broilers. International Journal of Poultry Science. 4:713–717.

Rajan K et al., 2017. Current aspects of salmonella contamination in the US poultry production chain and the potential application of risk strategies in understanding emerging hazards. Critical Reviews Microbiology 43:370–92.

Ram PK et al., 2007. Risk factors for typhoid fever in a slum in Dhaka, Bangladesh. Epidemiology and Infection 135(3):458-65.

Ramsden AE et al., 2007. The SPI-2 type III secretion system restricts motility of Salmonella-containing vacuoles. Cell Microbiol*ogy* 9(10):2517-29.

Rana K et al., 2021. Association of quorum sensing and biofilm formation with Salmonella virulence: story beyond gathering and cross-talk. Arch Microbiol*ogy* (10):5887-5897.

Rasheed MK et al., 2019. Extensively drug-resistant typhoid fever in Pakistan. Lancet Infectious Diseases 19(3):242-243.

Rashid K et al., 2023. Identification of Multiple Variant Extensively Drug-Resistant Typhoid Infections across Pakistan. American Journal of Tropical Medicine Hygiene 108(2): 278-284

Reda FM et al., 2021. Use of biological nano zinc as a feed additive in quail nutrition: biosynthesis, antimicrobial activity and its effect on growth, feed utilisation, blood metabolites and intestinal microbiota. Italian Journal of Animal Science 20(1): 324-335.

Rybak MJ, 2004. Resistance to antimicrobial agents: An update. Pharmacotherapy 24:203S-15S.

Saeed M et al. 2020. Extended-spectrum beta-lactamases producing extensively drug-resistant Salmonella Typhi in Punjab, Pakistan. Journal of Infection in Developing Countries 14(02): 169-176

Salem HM et al., 2021. Evaluation of the effects of silver nanoparticles against experimentally induced necrotic enteritis in broiler chickens. International Journal of Nanomedicine 6783-6796.

Saylers AA and Whitt DD, 2005. Revenge of the Microbes: How Bacterial Resistance is Undermining the Antibiotic Miracle. ASM, Washington, D.C.

Schwarz S and Chaslus-Dancla E, 2001. Use of antimicrobials in veterinary medicine and mechanisms of resistance. Veterinary Research 32: 201–225.

Seif Y et al., 2019. Systems biology and pangenome of *Salmonella* O-antigens. mBio. 10: e01247-19.

Shang Y et al., 2015. The effect of dietary fructooligosaccharide supplementation on growth performance, intestinal morphology, and immune responses in broiler chickens challenged with Salmonella Enteritidis lipopolysaccharides. Poultry Science 94(12): 2887-2897.

Shi C et al., 2015. Molecular methods for serovar determination of *Salmonella*. Critical Reviews in Microbiology 41: 309-25

Shivaprasad HL et al., 2013. Salmonella infections in the domestic fowl. In Salmonella in domestic animals (pp. 162-192). Wallingford UK: CABI.

Spackova M et al., 2019. Typhoid fever in the Czech Republic and an imported case after return from the Rainbow Gathering in Italy. Epidemiology Microbiology Immunology 68: 47-50.

Thung TY et al., 2018. Prevalence, virulence genes and antimicrobial resistance profiles of Salmonella serovars from retail beef in Selangor, Malaysia. Frontiers in Microbiology 8: 2697.

van der Wielen PW et al., 2000. Role of volatile fatty acids in development of the cecal microflora in broiler chickens during growth. Applied and Environmental Microbiology 66(6): 2536-2540.

Vindigni SM et al., 2007. Prevalence of foodborne microorganisms in retail foods in Thailand. Foodborne Pathogen Diseases 4(2): 208-215.

Wales AD et al., 2010. Chemical treatment of animal feed and water for the control of salmonella. Foodborne Pathogens and Disease 7:3–15.

Wang J et al., 2022. Aleri An Abattoir-based study on the prevalence of Salmonella fecal carriage and ESBL related antimicrobial resistance from culled adult dairy cows in Wuhan, China. Pathogens 9 (10): 853-853.

Watkins LKF, et al. 2020. Update on extensively drug-resistant Salmonella serotype *Typhi* infections among travelers to or from Pakistan and report of ceftriaxone-resistant Salmonella serotype *Typhi* infections among travelers to Iraq-United States, 2018-2019. Morbidity and Mortality Weekly Report (MMWR) 69(20): 618.

Whiley H and Ross K, 2015. Salmonella and eggs: from production to plate. International Journal of Environmental Research and Public Health 12(3): 2543-2556.

White DG et al., 2000. Characterization of chloramphenicol and florfenicol resistance in Escherichia coli associated with bovine diarrhea. Journal of Clinical Microbiology 38: 4593–4598.

Wibisono FM et al., 2020. A review of salmonellosis on poultry farms: Public health importance. Systematic Reviews in Pharmacy 11(9): 481-486.

Wigley P, 2014. Salmonella enterica in the chicken: how it has helped our understanding of immunology in a non-biomedical model species. Frontiers in Immunology 5: 482.

Wizemann TM et al., 1999. Adhesins as Targets for Vaccine Development. Emerging Infectious Diseases 5(3): 395-403

Wolfson JS and Hooper DC, 1989. Fluoroquinolone antimicrobial agents. Clinical Microbiology Reviews 2: 378–424.

Worku W et al., 2022. High prevalence and antimicrobial susceptibility pattern of Salmonella species and extended-spectrum β-lactamase producing Escherichia *coli* from raw cattle meat at butcher houses in Hawassa city, Sidama regional state, Ethiopia. Plos One 17(1): e0262308.

World Health Organization (WHO) 2011. Drug-resistant Salmonella. Fact sheet, No. 139. Accessed Oct 2011.

World Health Organization (WHO) 2017. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Journal of Medical Society 2017: 1-7.

World Health Organization (WHO) 2019. Drug resistant Salmonella infections in Pakistan: update. Weekly Epidemiological Monitor 12: 1.

Xu H et al., 2021. Characterization of *Salmonella* serotypes prevalent in asymptomatic people and patients. BMC Infectious Diseases 21: 632.

Xu ZR et al., 2003. Effects of dietary fructooligosaccharide on digestive enzyme activities, intestinal microflora and morphology of male broilers. Poultry Science 82(6): 1030-1036.

Yaqoob MU et al., 2021. The potential mechanistic insights and future implications for the effect of prebiotics on poultry performance, gut microbiome, and intestinal morphology. Poultry Science 100(7): 101143.

Yavari L, 2012. Antibiotic resistance in Salmonella enterica and the role of animal food control: A literature review of Europe and USA.

Yousry C et al., 2020. Integrated nanovesicular/self-nanoemulsifying system (INV/SNES) for enhanced dual ocular drug delivery: statistical optimization, *in vitro* and *in vivo* evaluation. Drug Delivery and Translational Research 10: 801-814