The toxic effect of antibiotic resistant Salmonella heidelberg on food poisoning in poultry products. —A Review

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Abstract: *Salmonella* is a widespread pathogen that is responsible for the food-borne infection salmonellosis. *Salmonella* infection is spread through food contamination mainly, especially poultry and dairy products. There are multiple mechanisms of action that cause the salmonellosis related symptoms such as fever, gastroenteritis, and abdominal pain. Among those mechanisms are the *Salmonella* virulence factors such as the Type I secretion systems, Fimbriae, Superoxide dismutase, and Ion acquisition. Also, the presence of Lipopolysaccharides (LPSs) which is the main component of the cell wall of Gram-negative bacteria contribute to the intestinal inflammation and Kupffer cells depletion in the liver. Some of the serovars of *Salmonella enterica* subsp. *enterica* such as *Salmonella heidelberg* were shown in more than one CDC outbreak to be a multidrug-resistant organisms that cannot be killed or controlled by antibiotics. The aim of this review is to discuss the mechanisms of *salmonella* toxicity and the prevalence of a multidrug-resistant *Salmonella heidelberg*.

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1. Introduction

Salmonellosis is a high prevalent foodborne illnesses caused by pathogenic *Salmonella* bacteria (CDC, 2018). Every year in the united states, more than million peoples are infected with salmonellosis, including 23,000 hospitalizations, and 450 deaths (CDC, 2018). Among the two *salmonella* main species, *Salmonella enterica* is the specie that is highly associated with human illness (Chiu, Su, & Chu, 2004). *Salmonella enterica* is a facultatively anaerobic gram-negative rod-shaped bacteria that is known to be non-spore-forming and highly infectious organism (Montville, Matthews, & Kniel, 2012). *Salmonella enterica* subsp. *enterica* is a subspecies of *Salmonella enterica* that includes many pathogenic serovars such as *Salmonella heidelberg*, *Salmonella typhi*, *Salmonella enteritidis*, etc. (CDC, 2011).

Moreover, a number of *Salmonella enterica* subsp. *enterica* serovars have been proven to be a multidrug resistant (MDR) bacterial strains; salmonellosis caused by these strains is a great threat due to its detrimental impact on people with impaired immune system, acquired immunodeficiency syndrome (AIDS), and older adults (Joshi, et al., 2009). In addition, there are high numbers of outbreaks related to domestic food supply contamination and livestock infection due to multidrug resistant *Salmonella* serovars in the last years (CDC, 2018; Joshi, et al., 2009). Out of the anti-drug resistant *Salmonella enterica* serovars, *Salmonella heidelberg* is a bacterium that can cause serious infection in poultry, dairy calves, and humans (APHIS, 2018). The aim of this review is to discuss the toxicity, antimicrobial resistance, and association of *Salmonella heidelberg* infection with poultry products.

2. Mechanisms of *Salmonella* Toxicity

Typhoidal vs Non-Typhoidal Salmonellosis

Salmonellosis is generally diagnosed by gastroenteritis symptoms such as diarrhea, abdominal cramps, chills, etc. (Giannella, 1996). In addition to fever which can be sometimes life-threating in case of enteric fevers (Giannella, 1996). *Salmonella enterica* serotypes are sometimes classified based on their ability to cause typhoid fever into two categories: Non-typhoidal *Salmonella* and typhoidal *Salmonella* (Gal-Mor, Boyle, & Grass, 2014). Typhoidal *Salmonella* serovars such as *S. typhi*, *S. paratyphi*, and *S. sendai* are endemic in developing countries and the disease caused by these microorganisms is restricted to human (Gal-Mor, et al., 2014). The typhoidal disease is clinical manifested by symptoms such as, fever, chills, diarrhea, constipation, nausea, and hepatosplenomegaly) whereas non typhoidal symptoms are gastroenteritis in immunocompetent patients such diarrhea, chills, and abdominal pain; and invasive extraintestinal illness for immuno-incompetent patients (Gal-Mor, et al., 2014). Non-typhoidal *Salmonella* such as *S. heidelberg*, *S. enteritidis*, and *S. typhimurium* usually associated with a broad host organisms such as human, pets, and livestock animals; causing this infection to be prevalent worldwide (Gal-Mor, et al., 2014). Vi capsular polysaccharide, attenuated oral (Ty21a), and whole-cell killed bacterial vaccines are usually the methods of vaccination for typhoidal salmonellosis; on the contrary, there is no specific human vaccination available for non-typhoidal salmonellosis (Gal-Mor, et al., 2014).

Salmonella Invasive and Adhesion Factors

The pathogenesis of *Salmonella* occurs by achieving what is known as virulence factors (Giannella, 1996). These factors include the ability to a) the ability to colonialize and attach host cells (Fimbrial loci and superoxide dismutase secretions), b) complete lipopolysaccharide coat, and c) generate toxins (Giannella, 1996; Ibarra & Steele-Mortimer, 2009). Colonization factors such as Type I secretion systems, Fimbriae, Superoxide dismutase, and Ion acquisition are vital for *Salmonella* adhesion, survival and intracellular niche (Ibarra, et al., 2009). Type I secretion are proteins that secreted for surface adhesion; BapA and SiiE are the main surface-associated proteins for *Salmonella* (Ibarra, et al., 2009). Another factor for adhesion stability is Fimbriae which are a group of virulence factors that promote biofilm formation on the host cells (García-Pastor, Sánchez-Romero, Gutiérrez, Puerta-Fernández, & Casadesús, 2018). Among the wide range of *salmonella* fimbrial loci, *std* is an operon that allows the pathogen to bind to cecal mucose in the large intestine leading to inflammatory bowel disease (García-Pastor, et al., 2018). According to Chatti, Messaoudi, Mihoub, and Landoulsi (2011) superoxide dismutase is an enzymatic cellular defense of pathogens against the damaging effects of reactive oxygen species (ROS) produced by immune system cells as a primary defense mechanism. DNA methylation has proven to a vital factor in that oxidative response by affecting the gene expression of superoxide dismutase and accordingly pathogenesis of salmonella (Chatti, et al., 2011). For *Salmonella enterica* to overcome iron deficiency in the eukaryotic host which usually occurs due to iron-binding proteins; siderophores such as enterobactin and salmochelin are released (Ibarra, et al., 2009). In addition to iron, Zn (II) is another element that *salmonella* is able to overcome its deprivation in host via ZnuABC transporter system. ZnuABC inactivation can result in lower *Salmonella* pathogenesis and virulence (Ilari, et al., 2016). Lastly, all the mentioned virulence and invasive factors lead to gastroenteritis and acute intestinal inflammation, in addition to alteration in the microbiota through nutrients and ethanolamine utilization (Thiennimitr, et al., 2011).

Lipopolysaccharides and Salmonella Toxicity

Lipopolysaccharide (LPS) are large molecules which consists of lipids (highly acylated lipid A) and repeated sugar polymer (O-antigen) where both sides are connected with an oligosaccharide Kdo/heptose core (Zhang, Meredith, & Kahne, 2013). The Gram-negative bacteria's outer membrane is formed from lipopolysaccharide layer which provides structural and protective support, especially from antibiotics, bile salts and other hydrophobic compounds (Zhang, et al., 2013). As an endotoxin, lipopolysaccharides are responsible for many pathophysiological effects to human body when *salmonella* spp infect the GI tract, such as leucopenia, fever, shwartzman reaction, and gastroenteritis (Rezania, et al., 2011). The mechanisms of action of lipopolysaccharides as an endotoxin can be attributed to the (1) innate immune response initiated by the synthesis and release of proinflammatory cytokines, (2) hypovolemia resulting in arterial and venous dilation, (3) B Cell activation and signaling by binding of lipid A in lipopolysaccharides to Toll-like receptor (TLR4) proteins, (4) damage to the endothelial tissues (disseminated intravascular coagulation DIC) as a result of high bacterial proliferation, and (5) inflammation and possible depletion of liver Kupffer cells (Valvano, 2015; Zhang, et al., 2013; Minomo, et al., 2017; Nguyen-Lefebvre & Horuzsko, 2015).

3. *Salmonella enterica* subsp. *enterica* serovar Heidelberg

Prevalence of Salmonella heidelberg

Salmonella heidelberg is serovar of *Salmonella enterica* that have been highly associated with human and livestock infection especially poultry animals (Switt & Weller, 2017). The prevalence of *S. heidelberg* is common in north America and have been linked to many Centers for Disease Control and Prevention (CDC) outbreaks in the last years Table1 (Switt & Weller, 2017). Most of the *S. heidelberg* infections was shown to be multidrug-resistant (MDR) and was widespread among multiple states (CDC, 2018). According to the CDC, clinicians diagnosing patients with a non-typhoidal salmonellosis who have been exposed to livestock animals, farms, cattle, farm workers, should consider the possibilities of multidrug-resistant (MDR) *S. heidelberg* infection.

Salmonella Heidelberg Antibiotic Resistance

In many clinical cases, *S. heidelberg* has been proven to be resistant to multiple antibiotics and drugs. In an epidemiologic and laboratory analysis study by Gieraltowski et al. (2016) the *S. heidelberg* related salmonellosis and the potential antimicrobial resistance of the pathogen were investigated. The sample of the study was 634 case-patients that were identified through surveillance and were chosen based on pulsed-field gel electrophoresis (PFGE) from

March 1, 2013 through July 11, 2014. After the identification and case finding, epidemiologic investigation, product traceback and testing, and antimicrobial susceptibility testing; it was shown that majority of the patient consumed chicken before the illness and sixty-seven percent of the *S. heidelberg* isolated were drug resistant, including thirty-five that were multi-drug resistant. The authors of the study concluded that chicken farms and slaughtering environment could be the sources of the bacteria and genes responsible for antibacterial resistance as evidenced by the fact that multiple PFGE patterns were linked to different poultry products from diverse production plans.

Table 1. Multiple U.S *Salmonella* Heidelberg outbreaks linked to poultry and other livestock animals' products according to the Centers for Disease Control and Prevention (CDC).

Outbreak Source	**States**	**Case Count**	**Hospitalizations**	**Deaths**	**Year**
Different Kratom products	41	199	76	zero	2018
Contact with Dairy Calves	15	56	17	zero	2016
Tyson brand mechanically separated chicken	1 (Tennessee)	9	2	zero	2014
Foster farms brand chicken	29	634	241	zero	2013
Raw chicken	13	134	33	zero	2013
"Kosher broiled chicken livers" from Schreiber processing corporation	6	190	30	zero	2011
Ground Turkey	34	136	37	1	2010 - 2011

According to results from Diarra et al. (2014) 15 *Salmonella heidelberg* isolates were resistant to drugs such as amoxicillin–clavulanic acid, ampicillin, ceftriaxone, ceftiofur, and cefoxitin. samples were gathered from commercial poultry farms, Canada and analyzed by PFGE, and PCR techniques. The *invA* gene was detected 86 % of the isolates whereas none of them were shown to carry the *spvC* gene.

4. Conclusion

Salmonellosis is a highly prevalent disease, as the microorganism responsible for the disease *Salmonella* is in animal and human intestines and can contaminate many foods such as eggs, chicken, and meat. In the United States, *Salmonella enterica* subsp. *Enterica* is the main cause of salmonellosis infection with a rate of annual 1.2 million illnesses according to the CDC. The major problem in *salmonella* infection is that some serovars such as *S. heidelberg* are able to genetically protect themselves from different drugs and antibiotic leading to extended period of illness and severe complications which may be fetal for immunodeficient, immuno-incompetent, and immunocompromised patients. *Salmonella* serovars such as *S. heidelberg* has a high incidence and association with livestock animals in general and, in poultry particularly. More than a prevention procedure has been suggested such as maintain an optimum hygienic conditions, proper handling and refrigeration, and Good Manufacturing Practice (GMP). Probiotics as animal feed could be a solution for multi- drug resistant *S. heidelberg* reduction, and better alternative for common antibiotic drugs. In addition, probiotics contacting feed can maintain the homeostasis of livestock animals' microbiomes and accordingly overall animal health.

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