Challenges associated with ceftriaxone resistance in *Salmonella*

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**ABSTRACT**

*Salmonella* is the leading cause of typhoidal and non-typhoidal infections in the world. The entry of *Salmonella* into the bloodstream causes an invasive disease state, resulting to high morbidity and mortality rates, especially in children. Owing to the misuse of antibiotics, certain *Salmonella* serovars are multi-drug resistant and do not respond to traditional antibiotics, such as ampicillin and trimethoprim-sulphamethoxazole, presenting a significant challenge for healthcare practitioners in treating and controlling the spread of this disease. Therefore, expensive third-generation cephalosporins, such as ceftriaxone, are currently used to treat *Salmonella* infection. However, a novel serovar of *Salmonella* that resists ceftriaxone was recently identified in Saudi Arabia, indicating widespread *Salmonella* resistance. A comprehensive literature review on ceftriaxone resistance in *Salmonella* is therefore necessary to reflect upon current challenges. In this report, we provide a summary of *Salmonella* incidence, mechanisms of ceftriaxone resistance in *Salmonella*, and current treatment options.

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**Introduction**

Infectious diseases remain a major cause of morbidity and mortality. The rising numbers of pathogens, particularly *Salmonella* that have developed resistance to a wide range of treatment options have been widely studied (Davies and Davies 2010). *Salmonella* infections are becoming difficult to treat and manage due to the development of multi-drug resistance.

*Salmonella* is a gram-negative bacterium that affects warm-blooded animals worldwide (Velge et al. 2012). There are approximately 2,600 different serovars of *Salmonella* categorized as either typhoidal or non-typhoidal. *Salmonella enterica* serovar Typhi or *Salmonella enterica* serovar Paratyphi A, B, and C cause typhoid and paratyphoid fever, whereas, *Salmonella* serovars Typhimurium and Enteritidis cause non-typhoidal fever with symptoms of self-limiting gastroenteritis (Alexander et al. 2009; Velge et al. 2012; Eng et al. 2015; Smith et al. 2016). Typhoidal fever is endemic in the developing world and non-typhoidal disease is present worldwide. Infants and young children are more susceptible to *Salmonella* infections than adults (Eng et al. 2015; Smith et al. 2016).

*Salmonella* infection is usually caused by the ingestion of contaminated water or food. Once bacteria pass from the stomach to the intestines, they enter the cells lining the intestinal epithelium and migrate to the intestinal spaces of the lamina propria. Non-invasive *Salmonella* cause self-limiting acute gastroenteritis (Chen et al. 2013). Some *Salmonella* serovars are up taken by different phagocytes and rapidly spread to lymph nodes and move through the blood stream to the spleen and liver (Figure 1). Several factors facilitate the transmission of some *Salmonella* serotypes from the intestines to the blood stream (Velge et al. 2012).

*Salmonella* enters the host’s phagocytic and non-phagocytic cells by interacting with the receptors on host cell membranes using different mechanisms (additional details about the mechanisms concerning *Salmonella* entry into the host cell are described in other studies) (Valdez et al. 2009; Velge et al. 2012; Wiedemann et al. 2014). Once inside the cell, bacteria override existing signaling pathways to alter gene
expression and protein function to facilitate the invasion of epithelial cells and the survival and replication of Salmonella inside host cells. Salmonella might be protected from antibiotics, such as gentamycin, which cannot penetrate host cells. Therefore, Salmonella infection poses a significant burden on the healthcare system worldwide. It has been difficult to circumvent the spread of Salmonella since it is highly adaptable, has a high tolerance to environmental stress, is distributed widely, and has multi-drug resistance (Chen et al. 2013). In a recent study (under publication), we verified that ceftriaxone resistant was presented by a novel Salmonella serotype. This study provides strong evidence that ceftriaxone resistance is expressed in different clinical Salmonella isolates (15.3%) from Indian labor in Saudi Arabia.

In this review, we provide an overview of the mechanism of Salmonella treatment by ceftriaxone and shed light on the mechanism by which Salmonella may develop resistance against ceftriaxone. Furthermore, we present the challenges of ceftriaxone resistance in Salmonella with other treatment options.

**Incidence of Salmonella**

Salmonella infections are caused by both typhoidal and non-typhoidal serovars, which are one of the leading causes of morbidity and mortality around the world (Kariuki, Gordon, et al. 2015). Globally, in 2010 there were approximately 100 million cases of gastroenteritis due to Salmonella infection with 155,000 deaths (Figure 2(A)) (Majowicz et al. 2010). In addition, there were approximately 28 million illnesses and over 200,000 deaths caused by typhoidal Salmonella (Figure 2(B)) (Crump et al. 2004; Kariuki, Gordon, et al. 2015).

Africa has the highest incidence rate of non-typhoidal Salmonella infections, and a troubling link between invasive non-typhoidal Salmonella disease, malaria and HIV has emerged (Smith et al. 2016). In 2010, Africa had approximately 2 million cases of invasive non-typhoidal Salmonella infections, with the highest incidence in children and young adults, which resulted in approximately 600,000 deaths (Feasey et al. 2012; Ao et al. 2015). High rates of infection and death in both children and adults are partly due to co-infection with HIV or malaria (Takem et al. 2014; Ao et al. 2015; Oneko et al. 2015). Accordingly, a reduction in malaria infections has led in a reduction in invasive non-typhoidal infections; a similar trend is expected in the HIV population as well (Mtove et al. 2011; Ao et al. 2015). In North America each year, there are approximately 1.4 million cases of invasive non-typhoidal Salmonella infection; approximately 22% of these cases require medical attention (Voetsch et al. 2004).

Different factors facilitate the spread of salmonella illness in Eastern Mediterranean Region (EMR). However, multidrug-resistance to Salmonella is the main factor that responsible for an increase in human salmonellosis in EMR. Increased poultry production, active international livestock trade, weak surveillance and investigation of Salmonella outbreaks, and lack of restricted roles concerning food handling and processing also contribute to the rising incidence (Eng et al. 2015).

The most important factors of invasive typhoidal and non-typhoidal Salmonella infections include traditional first-line drugs (ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol) and adaptation to immune-suppressed patients, especially those with HIV (Ao et al. 2015). These factors are of global concerns due to the decreased susceptibility of Salmonella to other types of antibiotics, such as ciprofloxacin and ceftriaxone. In fact, The National Antimicrobial Resistance Monitoring System NARMS and Centers for Disease Control and Prevention
Figure 2. The global burden of Salmonella deaths and illnesses by region. A. Africa has the highest incidence of non-typhoidal death, while the typhoidal and paratyphoidal deaths are highest in the eastern Mediterranean region. The Southeast Asia has the highest rates of Salmonella illness (B). AFR: African Region; AMR: America Region; EMR: Eastern Mediterranean Region; EUR: European Region; SEAR: Southeast Asia Region; WPR: Western Pacific Region.

(CDC) have monitored the resistance of Salmonella from humans, animals, and food products since 1996 (Crump et al. 2011; CDC 2013). The World Health Organization (WHO) also established a specific project in 2000, termed the WHO Global Salm-Surv (WHO GSS) program, to perform global surveillance and study Salmonella antimicrobial resistance (Hendriksen et al. 2009).

The CDC reported that non-typhoidal Salmonella (NTS) resistance and extended-spectrum cephalosporins (ESCs) were 0.1% in 1996, 0.4% in 1997, and 0.5% in 1998 (Dunne et al. 2000; Yates and Amyes 2005; CDC 2013). However, NARMS indicated that NTS ceftriaxone susceptibility rates were 4.4% in 2002 and 2003, 3.3% in 2004 and 2007, and 2.9% in 2005 and 2010. Other studies have reported outbreaks, in a very wide range from 1998 to 2008, caused by the most abundant NTS serovars due to consumption of diverse food commodities, such as chicken, eggs, beef, fruit, and vegetables (Jackson et al. 2013). Therefore, it is necessary to understand the mechanism behind the ceftriaxone action and how Salmonella resists to develop a rapid and accurate therapeutic treatment against Salmonella.

Mechanism of treatment of Salmonella by ceftriaxone

β-Lactam antibiotics for Salmonella infection treatment are used to target bacterial cell walls and inhibit its activity (Wise and Park 1965). In response to drugs, synthesizing of the β-lactamase enzyme by bacteria leads to β-lactam resistance. This enzyme cleaves the β-lactam ring and inhibits activity of the antibiotic. The third-generation cephalosporin, ceftriaxone, has been extensively used for the treatment of invasive Salmonella infection (Al-Mashhadani et al. 2011).

Ceftriaxone is a cephalosporin that has a 72%–97% cure rate, and no relapses are observed with treatment over 8–14 days (Butler 2011). Ceftriaxone is highly potent against a wide range of gram-negative and gram-positive bacteria and has a mechanism of action similar to other β-lactam antibiotics and acts by inhibiting the peptidoglycan layer of the bacterial cell wall (Hall et al. 1981) (Figure 3). It contains a β-lactam ring that mimics the structure of the D-alanyl-D-alanine amino acid used to build peptidoglycan. The cross-linking of peptidoglycan polymers to construct the bacterial cell wall is collapsed by ceftriaxone, which leads to eventual bacterial cell lysis.
catalyzed by transpeptidases, penicillin-binding proteins. Due to the structural similarity of ceftriaxone with D-alanyl-D-alanine, transpeptidases irreversibly bind to ceftriaxone and neutralize their activity. Since transpeptidases are irreversibly inhibited, the final cross-linking of peptidoglycan cannot take place and the bacterial cell wall collapses, leading to bacterial cell lysis (Barriere and Flaherty 1984). The pharmacokinetic profile of ceftriaxone has a long elimination half-life of 5.8–8.7 h; this long half-life allows for once-daily dosing. Ceftriaxone is rapidly and completely absorbed and penetrates most body tissues and fluids (Barriere and Flaherty 1984; Patel and Kaplan 1984).

Mechanism behind the development of Salmonella resistance

Salmonella can become resistant to cephalosporins by overproducing cephalosporinases, enzymes that degrade cephalosporins. The majority of these cephalosporinases are extended-spectrum β-lactamases (ESBLs) and their genes are located on conjugative plasmids, either on transposons or integrons (Su et al. 2004; Michael et al. 2006; Chen et al. 2013) (Figure 4). Since ESBLs are located on mobile genetic elements that can spread horizontally between bacteria by obtaining ESBL genes from resistance bacteria, sensitive bacteria can acquire resistance to cephalosporins (Figure 4). In addition, the use of continuous antibiotics for therapeutic or preventative measures in farm animals plays an important role in the development of higher resistance rates (Li et al. 2007). Using genotyping and plasmid analysis, researchers have determined that both clonal dissemination and horizontal transfer of a resistance gene bla\textsubscript{CMY}–2 contribute to the cephalosporin resistance of Salmonella enterica strains (Su et al. 2003; Yan et al. 2003; Li et al. 2007). Other genes like bla\textsubscript{CTX–M–15}, bla\textsubscript{CTX–M–2}, bla\textsubscript{OXA–1}, and bla\textsubscript{TEM–1} confer resistance to beta-lactams, often found on a novel plasmid pKST313 that carried class 1 integrons (Kariuki, Okoro, et al. 2015; Olaitan et al. 2015).

To study the effect of ceftriaxone treatment on Salmonella strains containing the bla\textsubscript{CMY}–2 gene, researchers treated seven Salmonella enterica strains with ceftriaxone using a protocol that simulated patient treatment. Following treatment, all seven strains showed less sensitivity to ceftriaxone treatment; in addition, they had increased expression of antimicrobial resistance genes, bla\textsubscript{CMY}–2 and floR (Hamilton et al. 2012). Several evidences suggest that non-typhoidal Salmonella strains S. Choleraesuis and S. Typhimurium generate different types of hybrid virulence plasmids containing antibiotic resistance genes, increasing their ability to survive under unfavorable drug environments. The ability of Salmonella to integrate new resistance genes in its virulence plasmid poses a serious threat to public health.

To better understand the mechanism behind ceftriaxone resistance in Salmonella, researchers subjected increasing concentrations of ceftriaxone in nine clinical ceftriaxone-susceptible S. Typhimurium to create ceftriaxone-resistant strains to stepwise selection. They identified a silent mutation in the acrR gene that encodes for a repressor for the efflux pump; however, there were no mutations in the virulence-associated genes. Furthermore, an increase in the expression of the AcrAB-ToIC efflux pump was detected (Yang WC et al. 2016). In another study, the acquisition of ceftriaxone resistance was explored by isolating Salmonella enterica serotype Anatum and Escherichia coli from diabetic patients. Both bacteria were susceptible to ceftriaxone at first isolation; however, they developed resistance to ceftriaxone after two weeks of ceftriaxone treatment due to the in vivo acquisition of a plasmid containing the bla\textsubscript{CTX–M–3} gene (Su et al. 2003).

Figure 4. Overview of the mechanism of Salmonella resistance. Generations of different types of hybrid virulence plasmids associated with antibiotic resistance genes are responsible for Salmonella survival, even under unfavorable drug environments.

Ceftriaxone resistance in Salmonella

Emerging ceftriaxone resistance in typhoidal and non-typhoidal diseases is an alarming and challenging
concern for health practitioners (Salmon-Rousseau et al. 2016). Generally, most reported cases of resistance are due to *Salmonella* Typhimurium, *Salmonella* Enteritidis, and *Salmonella* Newport and result in non-typhoid fever. These serovars are the most prevalent serotypes in many countries, are spread worldwide, and are associated with resistance in both humans and animals (Arlet et al. 2006; Eng et al. 2015).

The first ceftriaxone-resistant *Salmonella* infection was acquired from cattle in a 12-year-old boy in the USA (Fey et al. 2000). Since then, several cases of ceftriaxone resistance have emerged worldwide. A 5-year study from 2005 to 2009 in Slovakia identified 10 ceftriaxone-resistant isolates among 858 total isolates (Majtan et al. 2010). A study of 174 patients conducted in India showed that 8% of the *S. Typhi* isolates were beta-lactamase producers and 12% were resistant to ceftriaxone (Kumar et al. 2008). In a study from Taiwan, *Salmonella enterica* serotype Oranienburg developed resistance against ceftriaxone during treatment (Yang WC et al. 2016). While the rate of efficacy of ceftriaxone is very high against *Salmonella* infections, new cases of *Salmonella* serovars resistance are emerging worldwide, with over 43 countries reporting cases; several cases of ceftriaxone resistance have been reported in the USA, France, Spain, Italy, Turkey, Kenya, Western Kenya, Saudi Arabia, the Middle East and Central Asia, Pakistan, Bangladesh, India, Taiwan, and China (Yildirmak et al. 1998; Saha et al. 1999; Nastasi et al. 2000; Cruchaga et al. 2001; Yan et al. 2002, 2003; Egorova et al. 2008; Crump et al. 2011; Zaki and Karande 2011; Medalla et al. 2013; Wong et al. 2013; Zowawi et al. 2013; Krueger et al. 2014; Qamar et al. 2014; Rahman et al. 2014; Yang B et al. 2014; Kariuki, Okoro, et al. 2015; Olaitan et al. 2015; Onoko et al. 2015). The rates of resistance in *Salmonella* to ceftriaxone are shown in Table 1.

In regions with a large immigrant population, such as the Gulf Cooperation Council (GCC), USA, and UK, most ceftriaxone-resistant strains are imported from regions with a high prevalence, such as Africa, India, Pakistan, Bangladesh, and, particularly, southeast Asia (Saha et al. 1999; Rotimi et al. 2008; Kumarasamy et al. 2010; Van et al. 2012; Zowawi et al. 2013). Therefore, global transportation has played an important role in the spread of antimicrobial resistance when people travel from regions where the risk for the acquisition and dissemination of infectious diseases is high to regions with lower levels of infectious diseases (van der Bij and Pitout 2012). The Hajj pilgrimage in Saudi Arabia gathers 2–3 million people from over 180 countries annually, with documented cases of outbreaks of several infectious diseases (Olaitan et al. 2015). A number of respiratory tract infectious diseases, such as MERS-CoV, whooping cough, and pyogenic pneumonia, have been reported, in addition to common outbreaks of waterborne infections, including gastroenteritis (Salmon-Rousseau et al. 2016).

Furthermore, some *Salmonella* serotypes that are resistant to a third-generation antibiotic ceftriaxone have also been discovered in pilgrims from Hajj (Olaitan et al. 2015). In fact, these travelers act as carriers for *Salmonella* serovars resistant to ceftriaxone and then spread these serovars across different regions of the world. In a recent study, 102 non-typhoidal *Salmonella* serotypes (B or D) were isolated from 1,696 children. Resistance to ceftriaxone emerged in 6.2% in 2009 and 2010; however, the rate of resistance increased to 56.5% in 2012 and 2013 (Onoko et al. 2015). Therefore, the spread of antimicrobial-resistant is a critical issue that must be addressed to implement effective public health interventions.

These resistance cases were associated with increased risk of invasive disease, longer hospital stay, and increased challenges in treatment, suggesting arise of *Salmonella* serovars that could be resistant to all available antibiotics; it is also an inevitable side effect of the use of antibiotics, since there is an arms race between

| Study                  | Location        | Year(s)  | Source               | Resistance rates |
|------------------------|-----------------|----------|----------------------|------------------|
| Yildirimak et al.       | Turkey          | 1994–1996| Non-typhoidal humans | 5%               |
| Nastasi et al.          | Italy           | 1990–1998| Non-typhoidal humans | 0.4%             |
| Cruchaga et al.         | Spain           | 2001     | Non-typhoidal humans | 0.2%             |
| Su et al.               | Taiwan          | 2003     | Non-typhoidal humans | 1.5%             |
| Krueger et al.          | USA             | 2006–2008| Non-typhoidal humans | 3.8%             |
| Majtan et al.           | Slovakia        | 2005–2009| Non-typhoidal humans | 1.1%             |
| Oneka et al.            | Africa          | 2009–2010| Non-typhoidal humans | 6.2%             |
| Olaitan et al.          | Saudi Arabia    | 2013     | Non-typhoidal humans | 56.5%            |
| Lin et al.              | China           | 2012–2013| Animals              | 10%              |
| Kumar et al.            | India           | 2008     | *Salmonella typhi*   | 12%              |
the adaptability of bacteria and the introduction of new antibiotics (Fullybright 2016). Furthermore, prolonged therapeutic use, improper dispensing, and mis-using antibiotics in livestock have been major factors in the emergence of antibiotic resistance bacteria.

Other treatment options

Historically, chloramphenicol, ampicillin, and trimethoprim-sulphamethoxazole were prescribed to patients to treat Salmonella infections; however, they are no longer used due to the emergence of plasmid-mediated resistance in Salmonella serotype Typhimurium or Newport (Su et al. 2004; Butler 2011). Since the 1980s, fluoroquinolones and cephalosporins have been the drugs of choice due to their efficacy against the multi-drug resistant strains of Salmonella. Ciprofloxacin, ofloxacin, and gatifloxacin are fluoroquinolones that were prescribed more often than cephalosporins due to their oral use and low cost. However, in the last decade, new strains of Salmonella have developed resistant to fluoroquinolones (Kariuki, Gordon, et al. 2015; Pham et al. 2016).

Several strains that developed resistance to ceftriaxone treatments are also showing resistance to other antibiotic treatments. For example, nine isolates of different S. Typhimurium are resistant to ceftriaxone; they are also resistant to ampicillin, chloramphenicol, cefuroxime, aztreonam, cefepime, sulfamethoxazole-trimethoprim, and cefpodoxime (Kariuki, Okoro, et al. 2015). Moreover, several cases of resistance against nalidixic acid have been reported, with resistance rates of 11% (Majtan et al. 2010; Krueger et al. 2014). The more recent drug for the treatment of Salmonella infections is azithromycin, which has a cure rate of 81%–100% and is a promising alternative to ciprofloxacin and ceftriaxone (Butler 2011; John 2011). Resistance rates are the lowest for azithromycin since several cases have begun to emerge of Salmonella serovars (Wong et al. 2013; Wong et al. 2014; Lin et al. 2015).

Future outlook

Antimicrobial resistance to Salmonella strains represents a huge burden on the health system worldwide, specifically in underdeveloped countries. While targets for non-typhoidal and typhoidal Salmonella have been identified, the detection process is not sensitive enough to identify small amounts of bacteria in the blood (Feasey et al. 2012). A promising method proposes to identify the chromosomal oriC locus common to all Salmonella enterica subspecies enterica serovars (Tennant, Zhang, et al. 2011).

A potential approach to target Salmonella is the development of a vaccine against typhoidal and non-typhoidal Salmonella strains, which worked well for cholera by using inactivated whole bacterial cells (Lebens et al. 2011). For typhoid fever, three different vaccines are currently recommended for travelers to endemic areas as follows: the Vi polysaccharide capsule-based vaccine, the live attenuated oral Ty21a vaccine, and the killed whole cell parenteral vaccine (Germanier and Fuer 1975; Tacket et al. 1986; Engels et al. 1998; Dave and Sefton 2015). A major drawback is that these vaccinations are unavailable for children under the age of 2 years, who are at high risk of infection in endemic areas (Zaki and Karande 2011). Furthermore, there are currently no vaccines against paratyphoid fever or non-typhoidal Salmonella disease; however, research is being carried out to address this particular problem. For nontyphoidal Salmonella, attenuated Salmonella enterica serovars Typhimurium and Enteritidis strains that can serve as live oral vaccines can be used for prevention. These vaccines have been tested in mice and have shown promising results, indicating that a highly effective, broad-spectrum vaccine against Salmonella can be developed (Tennant, Wang, et al. 2011). Since different Salmonella serotypes express immunologically distinct O sidechains, it will be challenging to create a multi-antigen vaccine or multiple vaccines targeting different serotypes. It should be a high priority to develop vaccines against typhoidal and nontyphoidal Salmonella strains to combat their deathly effects (Feasey et al. 2012; Martin 2012).

Conclusion

Patients with invasive typhoidal and non-typhoidal Salmonella infections require anti-microbial therapy. Due to the high rates of resistance to conventional drugs, such as ampicillin, chloramphenicol, and sulfamethoxazole-trimethoprim, the use of antibiotics for salmonellosis is now limited to ceftriaxone and azithromycin. The increase in rates of resistance to ceftriaxone is extremely worrisome and will result in patients relying solely on azithromycin. This trend will
likely cause an increase in the burden of *Salmonella* infections worldwide and higher rates of morbidity and mortality. This effect will likely worsen as *Salmonella* strains develop resistance to azithromycin and other bacteria acquire the resistance genes. Therefore, there is an imperative need to control the spread of *Salmonella*, avoid the misuse and overuse of antimicrobial agents, and accelerate the development of new treatment options against salmonellosis.

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