

Review on Salmonellosis

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Abstract: *Salmonellosis* is an infectious disease of humans and animals caused by organisms of the two species of *Salmonella* (*Salmonella enterica*, and *S. bongori*). Although primarily intestinal bacteria, and widespread in the environment and commonly found in farm effluents, human sewage and in any material subject to fecal contamination. *Salmonellosis* can be found worldwide but seems to be most common where intensive animal husbandry is practiced. Reservoirs also remain in wild animals. Some *Salmonella* are geographically limited. *Salmonella* species are transmitted via the fecal-oral route. The most common mode of transmission is ingestion of food or water that has been contaminated with human or animal feces thus; infection remains a distressing public health concern worldwide. The genetic make-up of the *Salmonella* strains permits their adaptation in various environments, including human, animal and non-animal hosts. This increases the difficulty in eliminating the bacteria. The emergence of antimicrobial resistance in *Salmonella* strains is a serious health problem worldwide. Moreover, these multidrug resistant (MDR) *Salmonella* strains poses a great challenge in terms of effective treatment of the infections caused by these strains. Several preventive measures have been proposed to stop the spread of *Salmonella* infection, like proper food and water sanitation, pasteurization of milk and other dairy products, and elimination human faces in the food production these, restriction of indiscriminate use of antibiotics in food animals is by far one of the most effective measures. The objective of this paper was to review on the epidemiology and zoonotic implication of *Salmonella* in human, as well the mechanisms of resistance of *Salmonella* for antimicrobial drugs.

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Introduction

Food born diseases are public health problem both in developing countries, and most of the world population suffers from such diseases each year. Among all out of break of food born diseases bacteria including salmonella are responsible for more than 90% of clinical disease. These Microorganisms may cause diseases in either of the two ways intoxication or replication of microorganisms. Intoxication involves pathologic changes in the host caused by toxin formed before ingestion of the microorganism while food born infection, on the other hand, results from replication of microorganisms after it has been ingested (WHO, 1988).

The infection of salmonella in animals is important because of the direct economic consequences attributable to mortality and morbidity. The greater importance is the human health consequences by direct or indirect contact with animals which constitute vast reservoir of *Salmonella* organism (Libby *et al.*, 2004). The economic losses also associated with investigation, treatment, and prevention of illness but also affect the whole food production chain (Wray and Davies, 2003; Radostits *et al.*, 2007). The disease in animals is characterized by one or more of the three major syndromes such as

septicemia, acute enteritis and chronic enteritis. Although their clinical patterns are not distinct, different *Salmonella* species tends to differ in their epidemiology (Carlton, 1998).

Salmonella infection remains a major public health concern worldwide, contributing to the economic burden of both industrialized and underdeveloped countries through the cost associated with surveillance, prevention and treatment of the disease (Crump *et al.* 2004). *Salmonella* strains are not detectable in certain clinical samples that contain small numbers of organisms (Flicker, 1987).

Antimicrobial resistance is a global problem in general, but it might be more severe in Ethiopia where there is lack of antimicrobial resistance assessments of *Salmonella*, lack of rigorous regulation of antimicrobials and incomplete treatment courses as the result of patient non-compliance (Beyene *et al.*, 2011). Antimicrobial resistance can increase the morbidity, mortality, and costs associated with disease. Moreover, it has social and economic consequences and requires strong scientific and public health efforts to improve the situation. The increase in the number of resistant and multiresistant (resistant to two and more antimicrobials) strains of bacteria has been recognized by the World Health organization (WHO) and health

authorities as one of the major problems in public health (Helmuth, 2001). The objective of this paper was to review on.

- The epidemiology of Salmonella infections in animals.
- The zoonotic implication of Salmonella in human, and.
- The mechanisms of resistance of Salmonella for antimicrobial drugs.

Taxonomy And Nomenclature

Salmonella was first isolated in 1855 from the intestines of pigs infected with swine fever by Theobald Smith. The bacterial strain was named after Dr Daniel Elmer Salmon, an American pathologist who worked with Smith. The nomenclature of *Salmonella* is controversial and still evolving. Currently, the Centers for Disease Control and Prevention (CDC) use the nomenclatural system of *Salmonella* recommended by the World Health Organization (WHO) Collaborating Centre (Popoff *et al.*, 2003).

The genus *Salmonella* belong to the family Enterobacteriaceae in which most of the intestinal pathogen of human and animal are classified (Teka, 1997). According to the current system used by the CDC, the genus *Salmonella* contains two species. These are *Salmonella enterica* (*S. enterica*) and *S. bongori* (Radostits *et al.*, 2007). *S. enterica* can be further classified into six subspecies based on their genomic relatedness and biochemical properties. *S. enterica* subsp. *Enterica*, *S. enterica* subsp. *Salamae*, *S. enterica* subsp. *Arizonae*, *S. enterica* subsp. *Diarizonae*, *S. enterica* subsp. *Houtenae* and *S. enterica* subsp. *Indica*. Currently, there are 2463 serotypes (serovars) of *Salmonella* of which *S. bongori* contain less than 10 serovars that are extremely rare while the remaining serovars belong to the *S. enterica* spp. (Laminar and Popoff, 1987).

Salmonella nomenclature was complex and scientists use different systems to communicate about this genus. However, uniformity in *Salmonella* nomenclature is necessary for communication between scientists, health officials and the public (Brenner *et al.*, 2000). CDC use names for serotypes in sub spp. Enteric (for example, serotypes *Enteritidis*, *Typhimurium*, *Typhi* and *Cholerae suis* and uses antigenic formula for unnamed serotype. The name usually refers to the geographic location where the serotype was first isolated to emphasize that they are not separate spp. The serotype name is not italicized and the first letter is capitalized. At the first citation of serotype the genus is given followed by the word "serotype" or "ser".

Microbiology and virulence of Salmonella

Salmonella is a rod shaped, Gram-negative facultative anaerobe that belongs to the family Enterobacteriaceae, most of the members of this genus

are motile by peritrichous flagella except *S. enterica* serovars Pollorum and *S. enterica* serovar Gallinarum and non motile strains resulting from dysfunctional flagella (Aoust, 1997). The virulence of *Salmonella* relates to the ability to invade host cells, replicate in them and resist both digestions by phagocytes and destruction by the complement component of plasma. Following adherence probably through fimbrial attachment, to the surface of intestinal mucosal cells, the bacteria induce ruffling of intestinal membranes (Salyers and Whitt, 1994).

The ruffling facilitate up take of the the bacteria in the membrane-bound vesicles, which often coalesce. The organisms replicate in these vesicles and are eventually released from the cells, which sustain only mild or transient damage. The complex invasion process is mediated by the product of a number of chromosomal genes, whereas growth within host cells depends on the presence of virulence plasmids. The toxic oxidative effects of free radical produced by phagocytes are minimized by the bacterial catalase and super oxide dismutase activities. Resistance to killing by complement is partially dependant on the length of O antigen chain of lipopolysaccharide (LPS). Long chain of LPS prevents the complement component of the membrane attack complex from interacting with and damaging the bacterial cell membrane (Salyers and Whitt, 1994).

The Epidemiology Of Salmonella In Animals

The epidemiology of Salmonellosis as a disease of animals and zoonosis is complex, which often make animals control of the disease is difficult. Animals are the reservoir of food born disease of salmonella (Molbak *et al.*, 2002.). The epidemiological patterns differ greatly between geographical areas depending on climate, population density, land use, farming practice, food harvesting and processing technologies and consumer habits (Radostits *et al.*, 1994).

Susceptibility And Distribution

All animals are at increased risk of developing salmonellosis if their normal flora is disrupted (Clark and Glyles, 1993). Young animals are more susceptible to Salmonellosis than older ones. Poor sanitation, overcrowding, unfavorable weather, parturition, parasitism, transportation and concurrent viral infections are all factors which predispose animal to clinical salmonellosis. Diseases caused by non-host specific *Salmonella* infection are uncommon and are usually seen in chickens, pullets or ducklings less than 2 weeks of age and rarely in birds over 4 weeks of age. Poll rum diseases are seen predominately in chicks less than 3 weeks of age (Wary and Davies 2002).

Members of the genus *Salmonella* are ubiquitous Pathogens found in human and their livestock, wild mammals, reptiles, birds, and insects (Davis *et al.*, 1990). As intestinal forms, the organisms are excreted

in the feces from which they may be transmitted by insects and other living creatures to large number of places; they may also be found in water, especially polluted water (Jay, 2000). Although primarily intestinal bacteria they are wide spread in the environment and commonly found in farm effluents, human sewage, and in any material subject to fecal contamination. Salmonellosis has been recognized in all countries but appears to be most prevalent in areas of intensive animal husbandry, especially Poultry and Swine production (Wray and Davies, 2003).

The distribution and importance of serovars in salmonellosis in human and animals vary over time usually quite unknown reasons (Radostits *et al.*, 1994). Some serovars maintain their dominant role over many years others, emerge or re-emerge or decrease over time (Aoust, 1997). Therefore, future of *Salmonella* infection in all species is continual fluctuation in the proportion of serovar involved (Jones *et al.*, 2004). It is common for a serovar to be introduced to country and to establish in one or more species, possibly as the predominant serovar and then to decline without any apparent reason or without intervention of public health or veterinary authorities (Jones *et al.*, 2004).

Source of infection and Transmission

Salmonella are carried in the intestinal tract and associated organ of most farm and wild animals. They are spread by direct or indirect means. Infected animals are the source of organisms which they excrete and infect other animals directly or indirectly by contamination of the environment, primarily feed and water supplies (Radostits *et al.*, 1994). Feed may be contaminated, during storage, by wild animals, specially rodents or birds. Flies and other insects have also been shown to be vectors of *Salmonella*. Contamination may also occur in the feed mill or during transport either to the mill or to the farm (Wary and Davies, 2003). Infection in cattle may also occur via other routs, including the respiratory tract, by inhalation of aerosols (Gay, 2003). However, the cycle of infection may be more complex in some animal population; in poultry for example, the primary source of infection may be contaminated feed, and subsequent spread may occur via feco-oral rout or from egg to chick in the hatchery (Gillespie and Timoney, 1981).

Salmonella and *Campylobacter* are the most frequently isolated food borne pathogens, and are predominantly found in poultry, eggs and dairy products (Silva *et al.* 2011). Other food sources that are involved in the transmission of *Salmonella* include fresh fruits and vegetables (Pui *et al.* 2011). In general, food animals such as swine, poultry and cattle are the prime sources of *Salmonella* infections. The slaughtering process of food animals at abattoirs is considered one of the important sources of organ and

carcass contamination with *Salmonella* (Gillespie *et al.*, 2005).

Salmonella may survive for long periods in infected feces and slurries. In most, uncompensated feces *Salmonella* may survive for 3 to 4 months in temperate climates and for longer period in hotter climates (Wray and Davies, 2003). Contaminated drinking water may facilitate the spread of *Salmonella* among farm animals, which often defecate in their drinking water. Infection by such water may occur dung flooding, contaminating the pasture (Wray and Davies, 2003).

Survivability of *Salmonella* in aerosols and *Salmonella* transmission between animals via aerosols is well documented (Harbaugh *et al.*, 2006.). There is likely a similar risk for airborne transmission of *Salmonella* from animals or the environment to humans. Kennel workers have been cautioned to take measures to reduce splashes of feces to the mouth when hosing or cleaning a kennel (CDC, 2001).

Carrier state

Salmonella are facultative intercellular organism that survives in the phagolysome of macrophage; they can evade the bactericidal effect of antibody and complement. Thus persistence of infection in animals and in the environment is important epidemiological features of salmonellosis. When an animal is infected with *S. duplin*, for example, it may become clinical case or an active carrier, passing organisms constantly in the feces. It may also become a latent carrier with infection persisting in lymph nodes or tonsils but no *Salmonella* in the faces, or even passive carrier which is constantly picking up infection the pasture or the calf pen floor, but is not invaded so that when it is removed from the environment the infection disappear. These animals probably multiply the *Salmonella* without becoming permanent carrier. The importance of the latent carriers is that they can become active carrier or even clinical case under stress, especially at calving time (Radostits *et al.*, 1994).

The status of chronic carrier is defined as the shedding of bacteria in stools for more than a year after the acute stage of *Salmonella* infection. Since humans are the only reservoir of typhoid *Salmonella*, carriers of *S. Typhi* and *S. Paratyphi* are responsible for the spreading of enteric fever in endemic regions, as the common transmission route is the ingestion of water or food contaminated with the feces of chronic carriers (Bhan *et al.* 2005).

Public Health Significance Of Salmonella

Source of Infection

Salmonellosis is a common zoonotic and food borne disease of humans. ((Voetsch *et al.*, 2004) Non-typhoid Salmonellosis is worldwide disease of humans and animals. Animals are the main reservoir, and

diseases are usually food born in humans, although it can spread person to person. (Acha and Szfers, 2001). Foods of animal origin, especially poultry and poultry products, are often involved in sporadic cases and outbreaks of human salmonellosis (Sanchez-Vargas *et al.*, 2011). He also quoted that poultry and poultry products are a common food borne illness vector and consistently among the leading animal sources of *Salmonella* that enter the human food supply. He also added that humans encountered this problem by consuming raw or undercooked food especially of poultry and egg product. Red meat and red-meat products are also recognized as an important source of human salmonellosis). (EFSA, 2009).

Dairy products are from animal origin, they may also be implicated in human food-borne salmonellosis. Usually milk and milk products are submitted to pasteurization, which kills *Salmonella* serovars. Milk-borne salmonellosis is therefore often related to the consumption of raw or inadequately pasteurized milk. However, *Salmonella* serovars may also contaminate dairy products after the pasteurization process (CDC, 2007e). Despite the strong link between food of animal origin and human salmonellosis, people may be infected by other ways, such as by cross contamination at home and commercial kitchens, through contact with other people, pets - especially dogs, cats and reptiles, as well as by ingestion of vegetables and fruits (EFSA, 2009).

Occurrence and the Diseases in Human

Salmonellosis is one of the most important human food-borne diseases. The occurrence is now frequently related to bad weather conditions like storms resulting in contamination of drinking water with sewage (Clark *et al.*, 1993).

Salmonellosis in human ranges from the generalized typhoid infection, through the less severe paratyphoid infection to mild gastro enteritis. The majority of serovars produce mild to severe gastroenteritis that only rarely becomes generalized and severe infections are most often encountered in very young, old or immunologically compromised patients. It is generally accepted that *Salmonella* gastroenteritis is a zoonotic disease, mainly contracted by consuming large numbers of *Salmonella* in food of animal origin or foods contaminated with animal products in which *Salmonella* are proliferated. There is however, convincing evidence not only that infection can be a sequel to the consumption of small doses but that direct person-to-person contact is involved in many outbreaks (Jones *et al.*, 2000).

Antimicrobial Resistances In Salmonella
Definition and General over view

Antimicrobials are substances that have significantly contributed to the prevention and treatment of infectious diseases in humans, as well as too many animal species. However, the excess or overuse of antimicrobials can generate genomic selective pressures to enable microbes to adapt and acquire resistance (Yang *et al.*, 2010.). Bacterial antibiotic resistance can be intrinsic or acquired. Intrinsic resistance is naturally occurring in the host, such as multidrug efflux pumps or physical barriers preventing the entry of the antibiotic. Acquired resistance involves spontaneous mutations and transfer of the resistance genes from other bacteria through transformation, conjugation or transduction (Hastings *et al.*, 2004.).

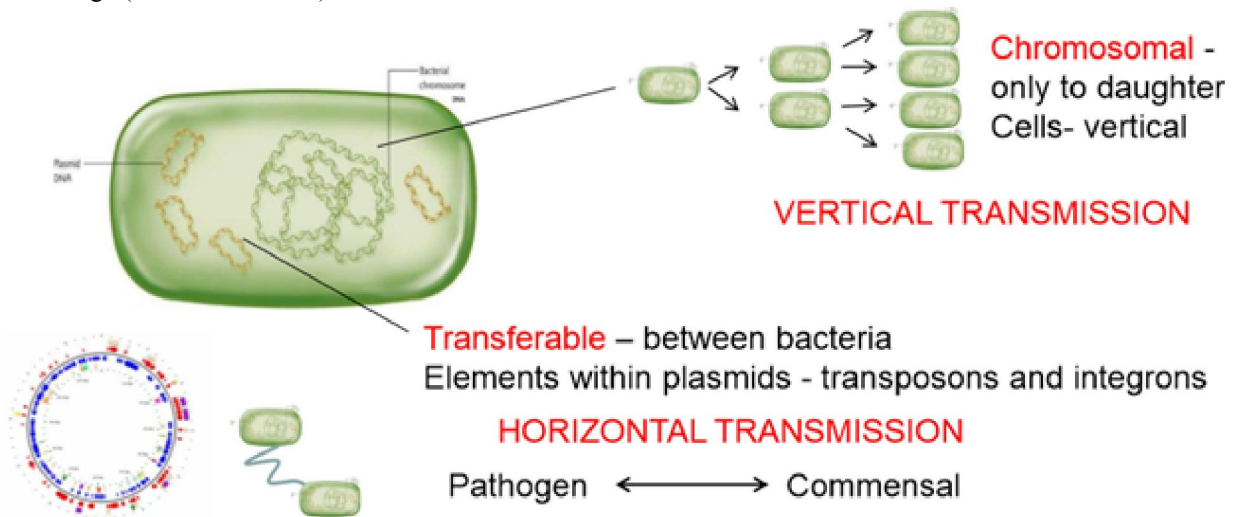


Figure 1. Transfer of the resistance genes among bacterial populations (Cook, 2016)

Antibiotic resistance genes were probably subjected to horizontal gene transfer even before

antibiotic era (Allen *et al.*, 2010). The routine practice of using antimicrobial agents to livestock to prevent

and treat disease is an important factor in the emergence of antibiotic resistant bacteria that are subsequently transferred to humans through the food chain. The potential pathways for antimicrobial

resistance relation to human, animal, food and environment explain below in Figure 2 (ACMSF, 1999).

Potential pathways for antimicrobial resistance

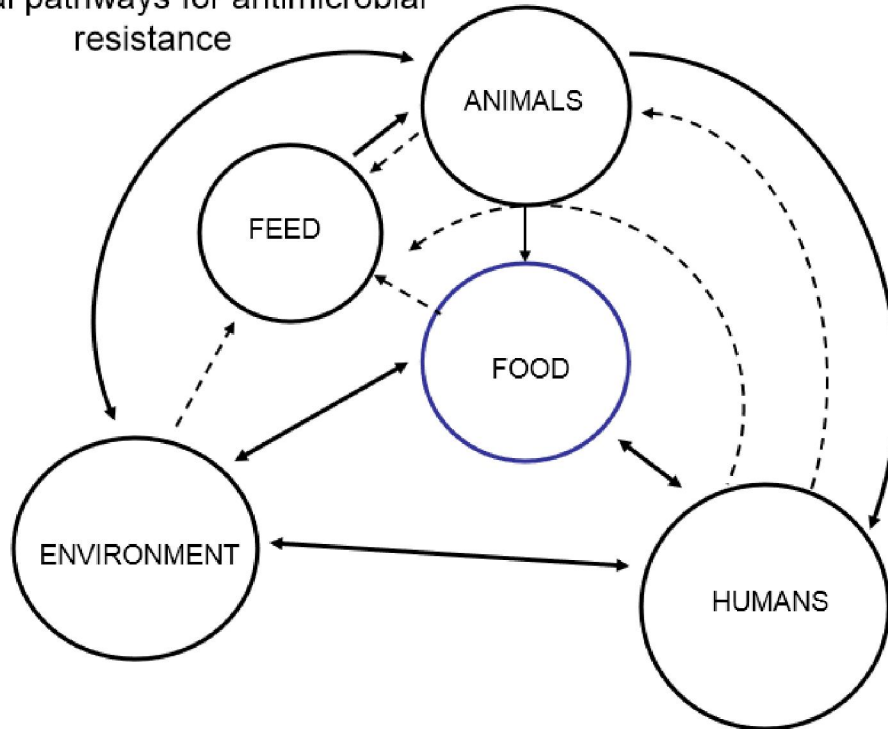


Figure 2. The potential pathways for antimicrobial resistance relation to human, animal, food and environment (ACMSF, 1999).

The effect of antimicrobials on an animal and its resident microorganisms will depend upon the dose level duration of administration and antimicrobial spectrum of the antimicrobial. The effect of antimicrobials to which *Salmonella* are sensitive at the therapeutic doses must be distinguished from the effect of the same antimicrobial at sub therapeutic concentrations and the effects at either concentration of antimicrobials to which *Salmonella* are intensive (Jones et al., 2004). Antimicrobial resistance can increase the morbidity, mortality, and costs associated with disease. Moreover, it has social and economic consequences and requires strong scientific and public health efforts to improve the situation. The increase in the number of resistant and multi resistant (resistant to two and more antimicrobials) strains of bacteria has been recognized by the World Health Organization (WHO) and health authorities as one of the major problems in public health (Helmuth, 2001).

Infections that involve the invasive sero types are often life threatening and require effective antibiotic treatment. Quinolones and cephalosporin poses a new challenge in treating infected patients, and the lack of an effective antibiotic therapy may lead to an increase in the morbidity and mortality rates. The emergence of MDR *Salmonella* has also resulted in the increased severity of bacterial infections in humans and animals. Epidemiological studies show that MDR *Salmonella* strains cause more severe or prolonged syndromes than susceptible strains, implying that the MDR strains are more virulent than the susceptible ones There also an association between drug resistant *Salmonella* and the routine clinical use of antimicrobials for infections other than salmonellosis (Radostits et al., 2007).

Mechanism of Resistance

Prior to the 1990s, the problem of antimicrobial resistance was never taken to be such a threat to the management of infectious diseases. But gradually treatment failures were increasingly being seen in

health care settings against first-line drugs and second-line drugs or more. Microorganisms were increasingly becoming resistant to ensure their survival against the arsenal of antimicrobial agents to which they were being bombarded (WHO, 2014). Resistance can be described in two ways as acquired or active resistance, the major mechanism of antimicrobial resistance, is the result of a specific evolutionary pressure to

develop a counterattack mechanism against an antimicrobial or class of antimicrobials so that bacterial populations previously sensitive to antimicrobials become resistant. This type of resistance results from changes in the bacterial genome. Resistance in *Salmonella* may be acquired by a mutation and passed vertically by selection to daughter cells (Yoneyama, 2006).

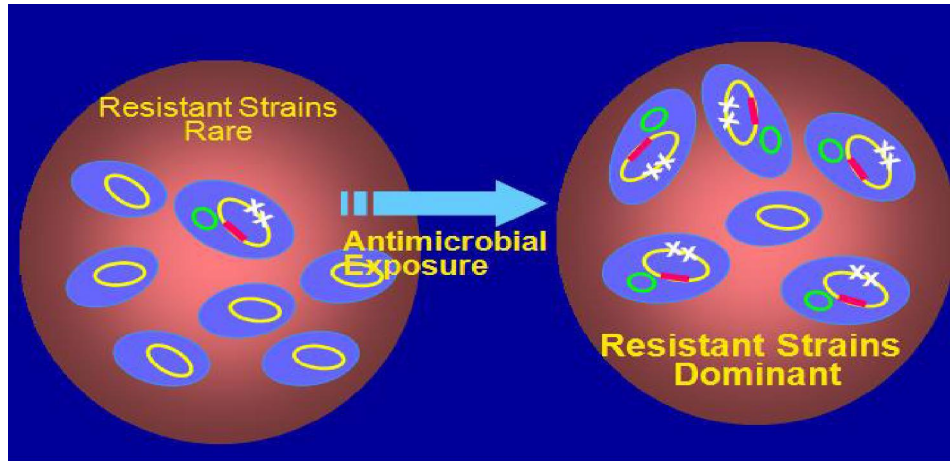


Fig 3. Development resistance in microorganisms (Yoneyama, 2006).

Exchange of genes is possible by transformation, transduction or conjugation (Yoneyama, 2006). Acquired resistance mechanisms can occur through various ways.

Mechanisms for acquired resistance the presence of an enzyme that inactivates the antimicrobial agents,

mutation in the antimicrobial target, which reduces the binding of the antimicrobial agent, reduced uptake of the antimicrobial agent, active efflux of the antimicrobial agent, overproduction of the target of the antimicrobial agent (Langton, *et al.*, 2005).

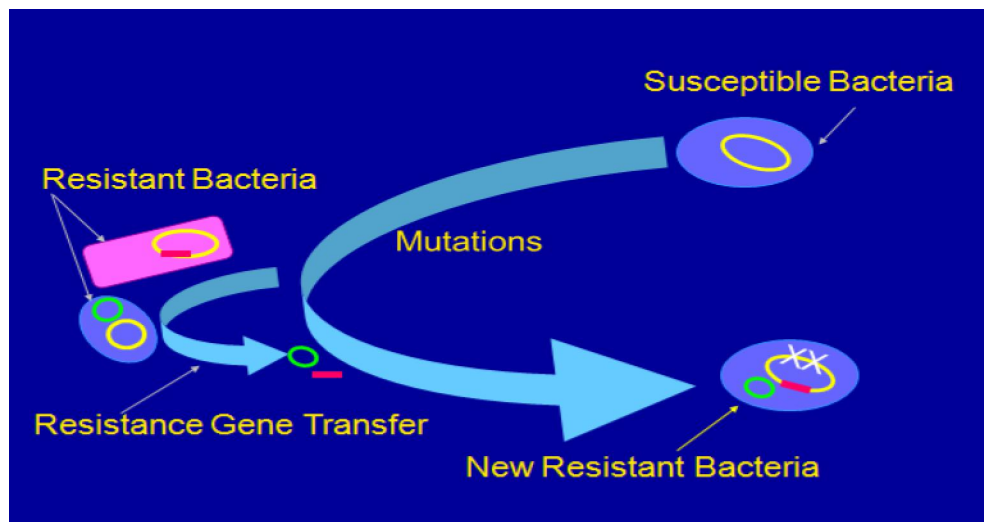


Figure 4. Emergence of Antimicrobial Resistance (Yoneyama, 2006)

Bacteria can be intrinsically resistant to certain antibiotics but can also acquire resistance to antibiotics via mutations in chromosomal genes and by horizontal

gene transfer. The intrinsic resistance of a bacterial species to a particular antibiotic is the ability to resist the action of that antibiotic as a result of inherent

structural or functional characteristics (Zhu, 2010). The serotypes of *Salmonella* displaying MDR phenotype have the ability to generate various types of hybrid plasmids. The majority of the gene cassettes located within these plasmids consists of resistance

genes that confer the antimicrobial resistance property of the serotypes against traditional antibiotics such as chloramphenicol, tetracycline, ampicillin and streptomycin (Guerra *et al.*, 2001, 2002).

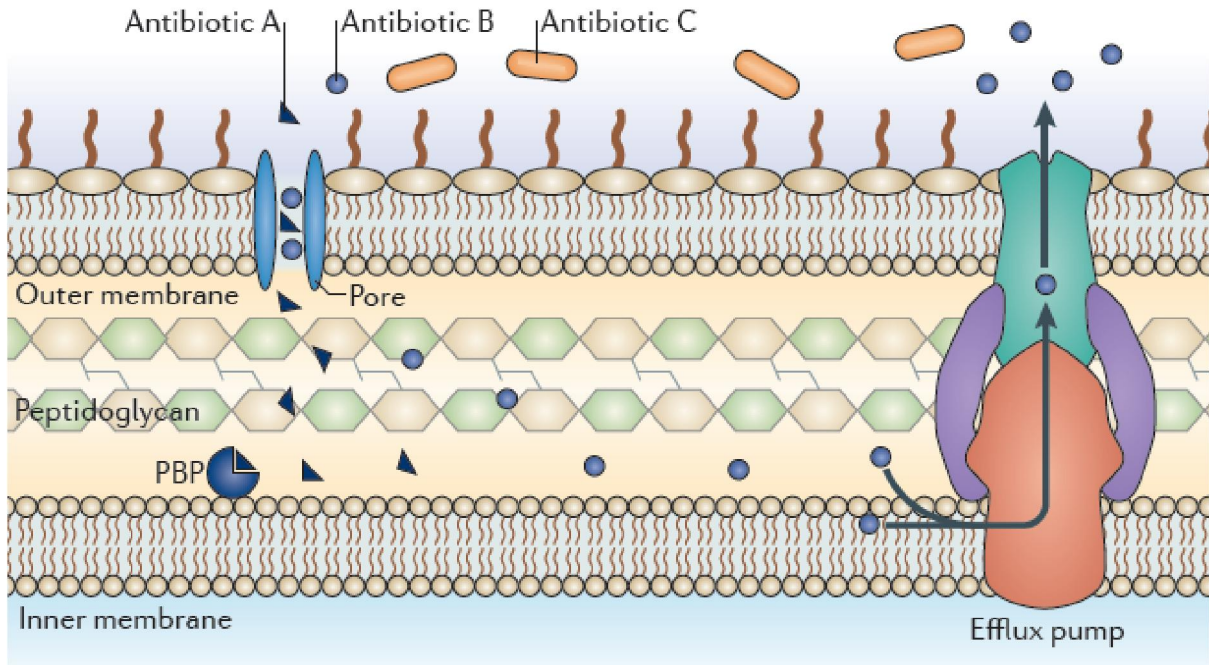


Figure 5. | Intrinsic mechanisms of resistance (Blake *et al.*, 2013).

The figure shows an overview of intrinsic resistance mechanisms. The example shown is of β -lactam antibiotics targeting a penicillin-binding protein (PBP). Antibiotic A can enter the cell via a membrane-spanning porin protein, reach its target and inhibit peptidoglycan synthesis. Antibiotic B can also enter the cell via a porin, but unlike Antibiotic A, it is efficiently removed by efflux. Antibiotic C cannot cross the outer membrane and so is unable to access the target PBP (Blake *et al.*, 2013).

Gram-negative bacteria have a lower proportion of anionic phospholipids in the cytoplasm membrane than do Gram-positive bacteria, which reduces the efficiency of the Ca^{2+} -mediated insertion of daptomycin into the cytoplasm membrane that is required for its antibacterial activity (Randal, 2013). Reducing the permeability of the outer membrane and limiting antibiotic entry into the bacterial cell is achieved by the down regulation of porins or by the replacement of porins with more-selective channels (Wozniak, 2010). Most antibiotics specifically bind to their targets with high affinity thus preventing the normal activity of the target. Changes to the target structure that prevent efficient antibiotic binding, but

that still enable the target to carry out its normal function, can confer resistance (Kumar, 2014).

Epidemiology and Drug resistance of *Salmonella* in Ethiopia

Antimicrobial resistance is a global problem in general, but it might be more severe in Ethiopia where there is lack of antimicrobial resistance assessments of *Salmonella* and lack of rigorous regulations, but there is easy access of antimicrobials for purchase of people without prescription and incomplete treatment courses as the result of patient non-compliance (Beyene *et al.*, 2011).

Therefore estimation of Salmonellosis is difficult because there is no *Salmonella* serotype and antimicrobial resistance surveillance and monitoring system (Dauris *et al.*, 2008). studies made on *Salmonella* isolation on food of bovine had not clearly documented so far in Ethiopia (Teshome *et al.*, 2012). Some part of Ethiopia where *Salmonella* is not routinely isolated and resistance to commonly used antimicrobial drugs in veterinary and public health sector not regularly assessed. Therefore, the present study, which was a part of cross-sectional study of *Salmonella* from supermarket food items and personnel, was undertaken to investigate the

susceptibility of Salmonella isolates to commonly used antimicrobial agents in Ethiopia for the treatment of bacterial diseases including salmonellosis. (Endrias et al.,2008). Antibiotic-resistant Salmonella infections of both human and animal are universal concerns, particularly in developing countries where the risk of infection is high because of unhygienic living conditions, close contact and sharing of houses between animals and human (Feasey.,2012).

Conclusion And Recommendation

Salmonella is most economically important diseases both in human and animals that remains a distressing public health concern worldwide. The genetic make-up of the *Salmonella* strains permits their adaptation in various environments, the multidrug resistance profile of reviewed studies indicated that many of the isolates were resistant to two or more commonly used antimicrobials. Misuse and overuse of antimicrobial drugs creates selective evolutionary pressure that enables antimicrobial resistant bacteria to increase in numbers more rapidly than antimicrobial susceptible bacteria and thus increases the opportunity of infection by resistant bacteria.

Based on the above conclusion, the following recommendations have been forwarded.

- Awareness should be created to the society about zoonotic important of the diseases.
- Veterinary and public health officials should work in liaison and exchange ideas on all aspects of salmonellosis and other zoonotic diseases prevailing in the country.
- Detailed epidemiological studies and sound surveillance of antimicrobial resistance must be made in Ethiopia.

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