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Review on Antibiotic Resistant Salmonella in Animals: Public Health and Economic Importance

Hordofa Noto*

School of Veterinary Medicine, Jimma University, Ethiopia

***Corresponding author:** Hordofa Noto, School of Veterinary Medicine, Jimma University, Ethiopia, Email: hordofanoto990@gmail.com

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Abstract

Salmonellosis is among the most common foodborne zoonotic diseases and problem of animal husbandry globally. Several classes of antibiotics such as β-Lactams, aminoglycosides, tetracyclines, phenicols, and sulphonamides are used to treat *Salmonella* infections. However, *Salmonella* serotypes can develop resistance against used antibiotics through different mechanisms of resistance. In most cases, antibiotics of the same families are used both in veterinary and human medicine. Thus, if *Salmonella* develops resistance to one of that antibiotic class, the resistance of the same antibiotics may be transferred to humans via direct contact of animal or consumption of animal products contaminated with resistant *Salmonella* species. In addition to impacts on public health and animal welfare, resistant *Salmonella* serotypes have negative economic effects. Hence, applying principle of antimicrobial stewardship and prudent use of antibiotics in both veterinary and human health sector is crucial to reduce the emergence and spread of antibiotic resistant *Salmonella* species. Therefore, the aim of this manuscript is to review the emergence of antibiotic resistant *Salmonella* in animals and its public health and economic significance. And also to review resistance mechanisms of *Salmonella* species and to discuss factors that drives antibiotic resistance.

Keywords: Acquired resistance, Antibiotics, Plasmid, Salmonella, Susceptibility, Transformation

1. INTRODUCTION

Salmonellosis is one of the most common foodborne zoonotic disease and global animal husbandry problem [1,2]. Salmonella cause foodborne poisoning in humans, mainly through consumption or contact of products of animal like pork, meat, and poultry products [3]. The infections of food animals with *Salmonella* serotypes play an important role in public health and particularly in food safety, as contamination of food products of animal origin are considered to be the major source of human *Salmonella* infections [4]. The primary habitat of *Salmonella* is an animal intestinal tract, but it is widely spread in the environment and commonly found in farm effluents, human sewage, and in any material subject to fecal contamination [5].

Antibiotic resistance is the ability of bacteria against the bacteriostatic or bactericidal effect of an antibacterial agent [6]. It is a global public health, animal health and welfare concern that influenced by both human and animal antibiotic use [7]. Inappropriate and unnecessary use of antibiotics has only increased the rate at which antibiotic resistant bacteria occur in communities and around the world [8]. The emergence of antimicrobial resistance in bacteria poses a significant challenge to both human and animal health since infections that are difficult to treat or untreatable increase with antimicrobial resistance, particularly as resistance to multiple antimicrobials increases [9]. Antibiotic resistant *Salmonella* is a major global public health issue due to the increase in resistance to both commonly used antibiotics and rise in multiple drug resistance [10].

Antibiotic resistant foodborne zoonotic pathogens like *Salmonella* in food-producing animals can spread to humans through consumption of contaminated food or water, and direct contact with animals [11]. Spread of resistance can involve the direct movement of resistant pathogenic bacteria from one ecological niche to another (e.g., between animal and humans) or by indirect means (e.g., via the food chain and water supply) [12]. Thus, the objectives of this manuscript are to review the emergence of antibiotic resistant *Salmonella* in animals, and its public health and economic importance. And also to review factors that drives antibiotic resistance.

2. GENERAL OVERVIEW OF ANTIBIOTIC RESISTANCE

In most part of the world, antibiotic resistance has reached highly hazardous level in both veterinary and human medicine and nowadays it recognized as emerging threat to public health and food security globally. The ability of bacteria to withstand bacteriostatic and/or bactericidal effect of one or more antibiotic agent at clinically attainable concentration that resulting in therapeutic failure is called antibiotic resistance [13]. Resistant bacteria have the ability to grow in presence of antibiotic concentration that would normally kill or suppress growth of susceptible bacteria [12]. Development of antimicrobial resistance by microbial pathogens and commensals represents a major threat to animal health and public health [14]. Just like in human health, although little is known about the level of problem, antibiotic resistance is also animal health concern [15]. Inappropriate use of antibiotics in food animals has a significant threat to human health as resistant pathogens from livestock enter the food supply and propagates in food products to humans [16]. As fresh meat products are mostly contaminated with commensal bacteria of livestock, if resistant, these commensal bacteria may serve as resistance gene reservoir that could be transferred to human pathogenic organisms [17] [18].

3. Category of Antibiotic Resistance

Resistance of bacteria to certain antibiotic groups can be natural or they can acquire resistance through variety of mechanisms [13]. The strategic ability of bacteria to resist effect of antibiotics is genetically encoded and resistance mechanisms are classified into intrinsic and acquired resistance [19].

Intrinsic resistance: It is the innate ability of bacteria against antibacterial effect of particular class of antibiotics through its inherent functional or structural characteristics [19]. This type of resistance is not associated with antibiotic use but it is due to the bacterial structural characteristics or the bacteria lacks structure of the antibiotic target or antibiotics not reaching its target site due to structural feature [6].

Acquired resistance: Unlike intrinsic, acquired resistance is the bacterial ability to resist antibacterial activity of a particular antibiotic agent to which it was susceptible previously. And this type of resistance is mediated by vertical (e.g., mutation) or horizontal gene transfer (e.g., transformation, transduction, or conjugation) through which bacterial genome is changed. These changes of bacterial genome results in alteration of functional or structural characteristics of bacteria which lead to resistance against antibiotics [19]. Chromosomal structures or extra-chromosomal genetic elements are the main causes of acquired resistance [6].

Chromosomal resistance*:* A chromosomal change due to mutation within single nucleotide base pair causes corresponding change in one or more amino acids, which consequently changes antibiotic affinity toward target site [19]. Bacterial mutation causes alteration of antibiotic target site receptors such as cell wall peptides, nuclear DNA or ribosomes to which the antibiotics bind. Because of that the antibiotics can no longer fit and the bacteria thus become resistant to the effects of antibiotics [20]. Mutations occur naturally due to errors during DNA polymerase, insertions, deletions and duplications [19] and this error can be a result of structural changes in bacteria [6].

Extra chromosomal resistance: It depends on extra-chromosomal genetic elements like plasmids, transposons and integrons that can be disseminated in different ways [6]. These genetic elements are responsible for carrying resistance genes [21] and they act as vectors transferring resistance genes between member of bacteria of the same species or to another species or genus [22].

Plasmid is a DNA fragment within a cell that is separated physically from chromosomal DNA and replicate independently and contains additional genes (e.g,resistance genes) that only benefits the survival of organisms under certain conditions [20]. Plasmid genes are responsible for enzymatic inactivation of antibiotics [6]. Transposon is a sequence of DNA that can change its position within genome, often creating or reversing mutation and changing the size of cells genome. Because of their mobility they also known as jumping genes and they can mobilize genetic material from bacterial chromosome to plasmid and vice versa [20].

Integron is responsible to catch and carry antibiotic resistance genes. They are relied on transposons to carry them around due to their immobility and they can transfer resistance genes from one bacterial species to completely different bacteria. In addition to this, they sometimes carry resistance genes for several antibiotics at same time. Therefore, misuse and overuse of less crucial antibiotics may results in selection pressure not only for themselves but also to other mostly important antibiotics [20].

Horizontal gene transfer is microorganism's self-genetic modification and is rapid, most relevant and very efficient way of transferring resistance between bacterial populations [20]. Three different mechanisms for horizontal gene transfer are transformation, conjugation and transduction [19].

Transformation is the uptake of DNA fragments from their surroundings and their homologous recombination in naturally competent bacteria [20,23]. Competent bacteria are those bacteria that have capability to pick up DNA fragments from their surrounding [24].

Exogenous DNA is picked up into recipient cell through cell membrane and incorporated into host cell chromosome via recombination, then finally resulting in genetic alteration of recipient bacteria [20].

Transduction is the process of transferring DNA from one bacterium to another through bacteriophage [19,20]. Compared to transformation and conjugation, it is less linked with transferring antibiotic resistance genes [19].

Unlike transformation and transduction, to transfer DNA between bacterial cells, conjugation involves cell-to-cell contact through sexual pilli. The donor bacteria has a genes responsible for sex pilli to be formed and through which DNA fragment that having resistance genes is transferred from resistant donor to previously susceptible recipient bacteria [19] see **Figure** 1.

4. Antibiotic Resistance Mechanisms in Salmonella

Mechanisms of antibiotic resistance in *Salmonella* species falls into (1) inactivation of antibiotic agent, (2) decreased permeability, (3) active efflux pump system, and (4) modification of target site and overproduction of target site in many serotypes to overwhelm antibiotics used [25].

Antibiotic inactivation: This is a common resistance mechanism that bacteria use to destroy or inactivates antimicrobial agents by enzymatic hydrolysis for inactivation of antibiotics [26]. The classical example of antibiotic inactivation is β-lactamases production that hydrolyze β-lactam ring in penicillin's, the enzyme inactivates antibiotics before they reaching their target site within bacteria [27].

Efflux of the antibiotics: Bacteria use this mechanism to extrude the toxic substances like antibiotics from the interior of their cells to external environment and it is major contributor for drug resistance [28].

Target site modification: Alteration of the target site of antibiotics makes the antibacterial unable to bind properly thus the bacteria evade action of antibiotics [29].

Reduced uptake of the antibiotic agent: Bacteria, including *Salmonella*, sometimes become resistant by reducing or preventing drug uptake through their cell membrane [26].

5. Resistance of Salmonella to Different Antibiotic Class

Antibiotic resistant *Salmonella* species counteract or inactivates the action of different antibiotics through its resistance mechanisms.

Resistance against aminoglycosides: Decreased uptake, modification of target site, decreased accumulation in bacteria and enzymatic inactivation of antibiotics are mechanisms of resistance to aminoglycosides. Enzymatic inactivation of aminoglycosides is the most common and important resistance mechanism exhibited by *Salmonella* species.

Adenyl transferases, acetyltransferases, and phosphotransferases are enzymes involved in aminoglycosides inactivation [30].

Resistance against β-lactams: β-lactamases that cleave β-lactam rings is the most common resistance mechanism conferred against β-lactams that preventing it from binding to and inactivating bacterial cell wall. Modification of target site and efflux system is also ways of resistance to β-lactams. In *Salmonella*, β-lactam resistance is encoded by horizontally acquired β-lactamases enzyme [30].

Resistance against phenicols: *Salmonella* resist the effects of chloramphenicol through inactivation with chloramphenicol acetyltransferases (CATs) enzyme [31]. Resistance to chloramphenicol can also be mediated through efflux pumps encoded by resistance genes *cml*A and *flo*R [32] [33]. Prevalence of chloramphenicol resistance is high in developing countries because of its easy accessibility and cheapness but it is banned in developed countries due to its toxicity [34].

Resistance against tetracycline: Bacteria resist the effect of tetracyclines through rRNA target modification, enzymatic inactivation, and efflux. Of these, active efflux is the most common resistance mechanism observed in *Salmonella* with resistance genes *tet*A, B, C, D, G and H [30].

Resistance against sulphonamides: Resistance to sulfonamides and its combinations (trimethoprim-sulfamethoxazole) in *Salmonella* is by acquisition of resistance genes encoding enzymes that do not bind sulfonamides and its combinations. The *sul* genes, *sul*1, *sul*2 and *sul*3 are responsible for encoding insensitive DHPS enzyme and which is detected in *Salmonella* globally [30].

Risk Factors for Emergence of Antibiotic Resistance

Emergence of antibiotic resistance is a natural response of bacteria to the exposure or presence of an antibiotic agent. Antibiotic resistant bacteria, including *Salmonella* species, is increasing due to factors such as misuse of antibiotics, unregulated antibiotic sales, incomplete use of antibiotics, inappropriate antibiotic prescription and dispensing practices, poor hygiene practices, animals number exposed to antibiotics, spectrum of antibiotics, duration and dose of antibiotics used [12], [34].

Transmission of Antibiotic Resistant Salmonella to Humans

Transmission of antibiotic resistant foodborne zoonotic pathogens such as *Salmonella* from livestock to humans is through consumption of contaminated food or through direct contact with animals or contaminated environment [11] [35]. Meat contamination with intestinal bacteria at slaughter is the main and most important route through which resistant bacteria reaches human [36]. In addition to animals and its product and waste contact, contaminated fomites also play a major role in spreading resistant bacteria locally and globally [37]. Resistant bacteria can be transmitted through any mechanisms that help bacteria to spread [13]. To be transmitted into humans, resistant bacteria of animal origin involves the spread via dissemination of resistant bacteria themselves (bacterial spread) or resistance gene spread (genetic spread) to potential pathogenic bacteria of humans [12].

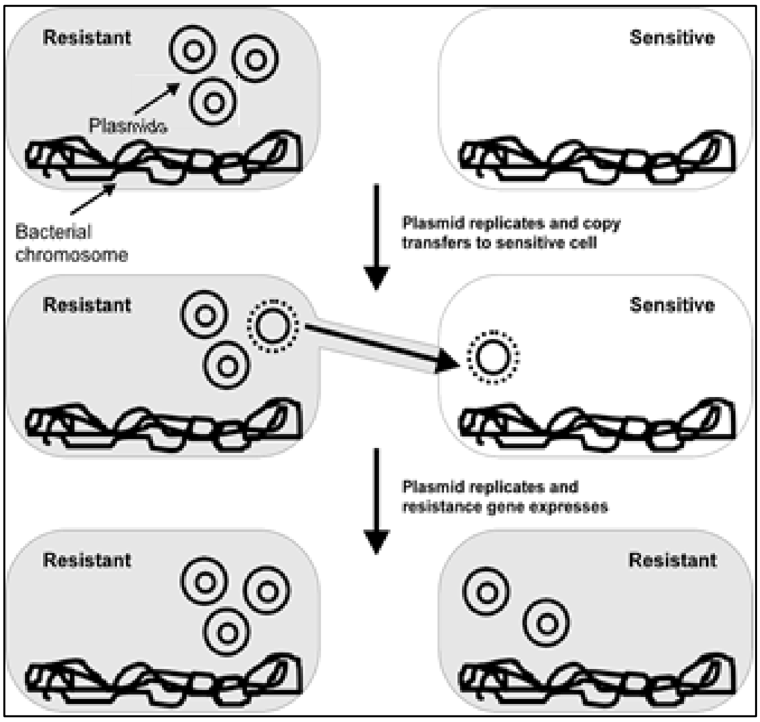


Figure 1: Antibiotic-resistance gene movement from bacteria-to-bacteria by conjugation [12].

The exchange of genetic elements carrying resistance genes between bacteria of the same or different serotypes or species facilitates the occurrence of resistant bacteria in environments where susceptible bacteria have the chance to mix with population of resistant bacteria, such as in animal or human gut, in pond and river, in slurry on agricultural soil and in aquatic environments [12] [37] [38] [39]. Thus, resistant commensal bacteria can donate its resistance genes to potentially pathogenic bacteria. As a result harmless bacteria that cannot induce a disease in humans can transfer its resistance genes to highly human pathogenic bacteria like *Salmonella*. The global spread of resistant bacteria like *Salmonella* has also been documented, and can occurs because of host (human or animals) movement or movement of contaminated products such as food and water from one place to other and even between country borders and continents [12].

6. Public Health Importance of Antibiotic Resistant Salmonella

Nowadays, World Health Organization (WHO) considered antibiotic resistant foodborne zoonotic pathogens like *Salmonella* as one of this century's leading global public health challenge [11] [35]. Misuse of antibiotics in food producing animals has a significant health threat to humans [16]. According to World Health Organization, antibiotic resistant bacteria can affect anyone of any age in any country [40]. Infections caused by resistant bacteria are difficult to treat compared to that caused by non-resistant bacteria and this makes it a concern for public health [41] [42]. Although antibiotic resistance in human pathogens arises from use of antibiotics in humans, resistant bacteria of animal origin such as *Salmonella* can infect human being. Highly exposed human groups such as farmers, slaughterhouse workers, cooks and animal product handlers have a higher ratio of resistant *Salmonella* in their feces than the general population [36]. Clinical and public health consequences of antibiotic resistant *Salmonella* species are failure in therapy, increased burden of illness and outbreaks [43], increase in virulence of *Salmonella* serotypes [44], increased morbidity and mortality [43] [45], increased treatment cost [46], longer stay in hospital which can also cause acquistion of nosocomial infections and increased resistant *Salmonella* transmission [43].

7. Economic Significance of Antibiotic Resistance

Antibiotic use in food animals has positive economic effects due to reduction of diseases that causes economic loss in farm and because of its role in prevention and control of potential zoonotic disease [47]. However, in contrast to antibiotic role in prevention and control of both pathogenic and zoonotic bacterial infections in animals, antibiotic resistance due to misuse and overuse of antibiotics in veterinary medicine has direct negative impacts on economic success of farm in addition to failure of treatment which directly affects animal health, productivity and welfare [48].

Economic importance of antibiotic resistance in case of public health is associated with long period of hospitalization, use of more expensive antibiotics,longer sick time of manpower, cost of research and development, and high mortality and morbidity of resistant organisms in both developing and developed countries [47] [49]. The influence of resistant pathogens on labor via productivity loss due to sickness and premature death is significant [50]. According to Taylor *et al.* [51], if current antibiotic resistance pattern is continued, in ten years, the global working age will be decreased by two years.

On economic perspectives of antibiotic resistance, if substantive efforts are not taken to tackle the effects of antibiotic resistance estimation of recent reports shows that about 10 million deaths and 100 trillion United State dollars of world's economic loss will occur in 2050 [52]. For instance, antibiotic resistance cost about 55 billion dollars (20 billion dollars for health care and 35 billion dollars for loss of productivity) in USA according to CDC estimation [53] [54]. A research by World Bank detected that poverty rate because of antibiotic resistance will be elevated and its impact is higher in low income countries compared to other countries [55].

According to the World Bank report, there will be a significant decrease in global exports by 2050 because of effects of drug resistance on labor intensive sectors [55]. Of these sectors, livestock output will be affected significantly [56]. Similar to humans, the effect of drug resistance on animals may be due to failure in therapy, morbidity and mortality, and severity of resistant pathogens [57]. These effects lead to decrement of production and livestock trade resulting in elevated prices of animal products such as meat, milk and eggs, which in turn results in economic loss [55] [57]. World According to the World Bank report, there will be a significant decrease in global exports by 2050 because of effects of drug resistance on labor intensive sectors [55]. Of these sectors, livestock output will be affected significantly [56]. Similar to humans, the effect of drug resistance on animals may be due to failure in therapy, morbidity and mortality, and severity of resistant pathogens [57]. These effects lead to decrement of production and livestock trade resulting in elevated prices of animal products such as meat, milk and eggs, which in turn results in economic loss [55] [57]. World Bank estimated that there will be 11% loss in livestock production by 2050 if current level of resistance is not slow down [55]. Such sufficient loss in livestock production will decline nation's income which in turn aggravates the situation of economy [57].

8. Diagnostic Methods of Antibiotic Resistance

Antibiotic resistance of individual bacterial isolates is detected by *in vitro* procedures known as Antibiotic susceptibility testing (AST), which can determine either a bacterial isolate is resistant or susceptible to an antibiotics and can also be used to monitor the emergence or spread of resistant bacteria [58]. The susceptibility testing methods can involves phenotypic testing which determines the response of bacterial isolates to an antibiotics when exposed, and genotypic testing which uses polymerase chain reaction (PCR) to detect resistance genes or plasmids [7].

Dilution method (broth and agar dilution) and disc diffusion (Kirby-Bauer) methods are examples of susceptibility testing methods. Of these methods, disc diffusion and broth micro dilution are most commonly used in veterinary laboratories [59].

To ensure repeatability of results and comparability of results based on compiled common data, standardized procedures should be followed by laboratories [7]. These standardized procedures, interpretative criteria and recommendations for susceptibility testing methods for veterinary pathogens are updated by certain organizations such as Clinical Laboratory Standards Institute (CLSI), OIE and Calibrated Dichotomous Sensitivity (CDS-AST) [60].

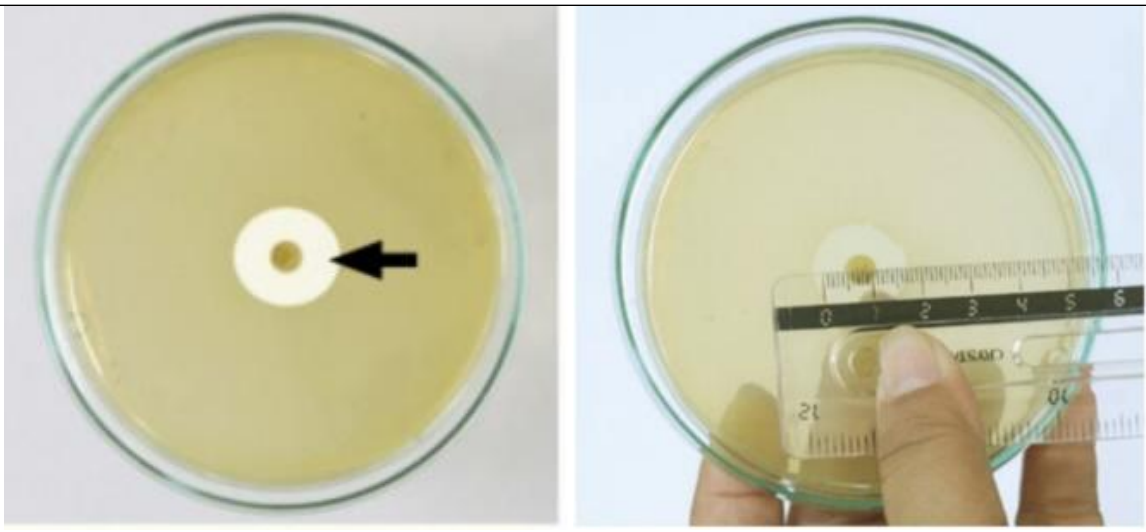
Disk-diffusion method: Involves application of drug impregnated disc of filter paper on an agar plate surface that has been inoculated with the bacteria of interest [61]. In disc-diffusion technique, the drug concentration is decreased logarithmically as the drug diffuse through the agar and as distance from disk is increased, which results in circular growth inhibition zone and the diameter of which is inversely proportional to minimum inhibitory concentration (MIC) [62]. Therefore, the larger inhibition zone, the lower antibiotic concentration is required to inhibit bacterial growth [63]. Zone of inhibition diameter shows an isolate susceptibility and rate of drug diffusion through agar medium [58].

The obtained growth inhibition zone is measured using caliper or ruler and recorded in millimeters (see **Figure 2**) [64]. The interpretation of diameter of zone of inhibition depends on the guidelines of Clinical Laboratory Standards Institute (CLSI) and accordingly the organisms are reported as either susceptible, intermediate or resistant [58]. As advantages, the test is reproducible, easy to perform and require no expensive equipment [64]. However, it can only be used to test rapidly growing organisms [62].

Dilution Method: Both of dilution methods (agar and broth dilution) are commonly used to determine minimum antibiotic concentration that kill (bactericidal effect) or inhibit growth (bacteriostatic effect) of bacteria [65]. For both of them, minimum inhibitory concentration (MIC) is the concentration at which an isolate is inhibited completely [66]. This *in vitro* test is used to classify the tested bacteria as susceptible, intermediate or resistant to the tested antibiotics and also considered as reference and used to evaluate the performance of other susceptibility testing methods [65].

Broth Dilution: Uses liquid growth medium containing geometrically increasing antibiotic concentration (twofold series), which is inoculated with defined number of bacterial cells [65]. This technique subject bacterial isolates to series of twofold antibiotic concentration, concentration of antibiotics in each test tube is usually double that of previous tube (see **Figure 3**) [66]. Tubes containing test organism and antibiotics are incubated under optimum conditions for 16 to 24 hours and interpreted based on the presence of turbidity or sediments, turbidity or sediment indicates growth of organism [65].

Agar Dilution: It uses agar medium that incorporated with varying antibiotic concentration which is usually serial twofold dilutions and followed by application of defined inoculum of bacteria to the surface of agar plate [67]. The presence of bacterial colonies on agar plates after incubation indicates the growth of bacteria [65]. Agar dilution test has advantages such as reproducible result and satisfactory growth of most non-fastidious organisms, however, it is not performed in routine clinical laboratories but it is ideal for regional reference or



(A) Zone of inhibition (B) Recording zone of inhibition diameter [64]

Figure 2: Disc-diffusion method of susceptibility test

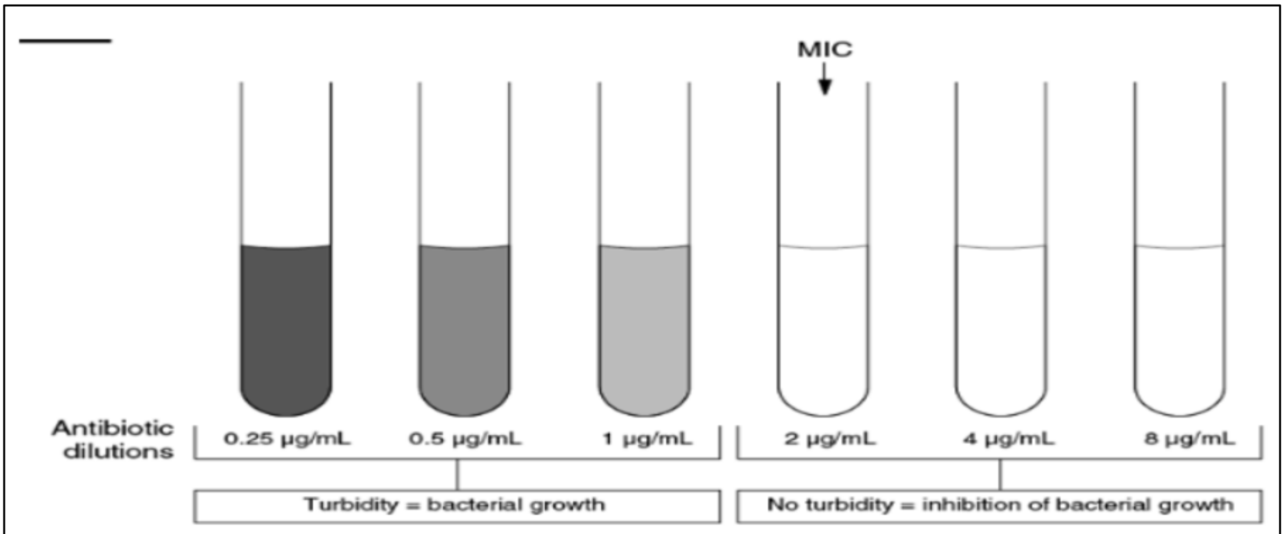


Figure 3: Broth dilution method diagram with series of twofold antibiotic concentration [66].

Or research laboratories that test large numbers of bacterial isolates [68].

9. Antibiotic Resistance Prevention and Control

Since antibiotic resistance is a complex issue, its mitigation requires the efforts of experts from animal, human and environmental heath to work together to minimize development and spread of resistance [69]. Thus, occurrence and spread of antibiotic resistance can be minimized by applying the principle of antimicrobial stewardship such as prudent use of antibiotics, treatment that based on antibiotic susceptibility testing result [70], and only using antibiotics in situations where failure to treat would compromise the health and welfare of patient [69]. According to WHO guidelines to prevent and control antibiotic resistance, antibiotics should only be given to animals under supervision of veterinarians, avoid antibiotic use in healthy animals, avoid antibiotic use as growth-promotant agent, vaccination, good hygiene practices when handling and processing foods of animal source, and improvement of biosecurity and animal welfare to avoid incidence of infections [40].

10. CONCLUSION

Salmonellosis is a foodborne zoonotic disease that can significantly bring public health and economic impacts. Humans acquire the infection through consumption of contaminated food of animal origin. Several antibiotics are used to treat salmonellosis in both veterinary and human medicine, but *Salmonella* serotypes may develop resistance against these antibiotics. Inappropriate use of antibiotics in both animal and human aggravates the problem further. Hence, infections caused by antibiotic resistant *Salmonella* strain become difficult to treat than infections caused by susceptible strains. Economic effects of antibiotic resistant *Salmonella* infection is significant due to the costs of diagnosis and treatment, use of expensive antibiotics to treat resistant strain, morbidity and mortality of infection both in human and animals, and restriction of trade on livestock products. Therefore, applying principle of antimicrobial stewardship and prudent use of antibiotics in both veterinary and human health sector is crucial to minimize the emergence and spread of antibiotic resistant *Salmonella* species.

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