Influencing factors of antibiotic resistance

By

Nosin Sharmili

15236010

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Declaration

It is hereby declared that

1. The thesis submitted is my original work while completing the degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material that has been accepted or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all the main sources of help.

Student's Full Name & Signature:

Nosin Sharmili
Student ID: 15236010

Approval

The thesis/project titled “Influencing factors of antibiotic resistance: a review” submitted by

1. Nosin Sharmili (15236010)

Fall, 2015 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Science in Biotechnology on [Date-of-Defense].

Examining Committee:

Supervisor:
(Member)

Fahim Kabir Monjurul Haque, PhD
Assistant Professor, Department of Mathematics and Natural Sciences
BRAC University

Program Coordinator:
(Member)

Iftekhar Bin Naser, PhD
Assistant Professor, Department of Mathematics and Natural Sciences
BRAC University

Departmental Head:
(Chair)

A F M Yusuf Haider, PhD
Professor and Chairperson, Department of Mathematics and Natural Sciences
BRAC University

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Nosin Sharmili

Student ID: 15236010

Abstract

Antimicrobial resistance (AMR) is the path in which microbes tends to support its survival. It is always not only about microbes there are bacteria as well for which antibiotic was invented. Then again there is also resistance to antibiotic. It is just like AMR, the way in which bacteria grows a support system for its survival.

Each year millions of people die because of antibiotic resistance. Once it used to cure people but slowly when it became resistance it is more harmful than useful now a days. Because these infections causes by bacteria are hard to treat. Higher does or going for alternate path could be more difficult to save a life and costly as well.

The factors which influence antibiotic resistance can be handled in a tricky way. For instance man made causes which includes overuse can be avoided easily. People should be more careful which drug they are taking because taking more antibiotic than need will slower the effect of it. It should only be taken when necessary. But again there is also abuse of prescription. Doctors have to be careful in need to save their patients. Then there is agricultural use, in which farmers should be educated by volunteers as well as general people. Practicing good health care will reduce diseases specifically infectious diseases. Like maintain good hygiene, hand washing, talking and maintaining about sexual transmitted diseases etc.

Main usage of antibiotic is divided into two, human and animals. Also the spreading causes of antibiotic resistance are these two characters. Pharmaceuticals plays a great role of dissemination of antibiotic. Especially the place where large amount of medicines are made. Selective pressure is created because antibiotic booster. The selective pressure in the population of bacteria is the cause of death of vulnerable bacteria. But growing reason of resistance bacteria. These resistance bacteria are not like other bacteria they have growth advantage and it multiplies faster. Now antibiotic resistance have become more prevalent also needing of alternate to resistant. Bacteria can have a growth advantage and proliferate faster than vulnerable bacteria even at very low levels of antibiotic.

Keywords: Antibiotic, Antibiotic resistance, Susceptible, selective pressure, multi drug.

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Chapter 1

Introduction

The term 'Antibiotic Resistance' rings a threatening bell worldwide due to public health, mortality rate. The medicines used to prevent and treat infectious diseases by bacteria, fungi, parasites are called antibiotics. Antibiotics plays significant role to treat and prevent bacterial infections.(Aslam et al., 2018; Lee Ventola, 2015) A report has been issued covering practice of microbes to protect against infectious diseases in ancient China, Greece, Egypt, although penicillin was discovered in 1928Trusted Source by Alexander Fleming's became modern use of antibiotics. (*Antibiotics: Uses, Resistance, and Side Effects*, n.d.; *Antimicrobial Resistance*, n.d.)

Antibiotic resistance happens when after long period of time naturally or by human's actions microbe's changes patterns and no longer respond to the medicine making it impossible to treat diseases.(Beckley & Wright, 2021; Lee Ventola, 2015; Sengupta et al., 2013; WHO, 2015) In today's news most concerned, dangerous and developing public health topic is antibiotic resistance. The World Health Organization (WHO) quotes "one of the biggest threats to global health, food security, and development today." (*Antibiotics: Uses, Resistance, and Side Effects*, n.d.; *Antimicrobial Resistance*, n.d.; *Global Action Plan on Antimicrobial Resistance*, n.d.; Aslam et al., 2018; WHO, 2015). Most common source of antibiotic resistance are divided into two, human and other animal.(*About Antibiotic Resistance | Antibiotic/Antimicrobial Resistance | CDC*, n.d.).

This article is to discuss about the influencing factors of antibiotic resistance. Which will cover most facts like natural causes and also man made causes.

Chapter 2

Antimicrobial resistance and it's Causes

A leading role for growing antibiotic resistance is played by pharmaceutical industry. The effluent, the waste and discards effect antibiotic resistant. Major role of pharmaceutical industry is played where large and bulk amount of drugs are made. Because of that antibiotic booster creates a selective pressure among bacterial population. In this population vulnerable bacteria dies but resistant bacteria survives. *(NPS: Better choices, n.d.)*. These bacteria continues growing and it has more power of growth advantage and multiply its population rather than other bacteria.(Gullberg et al., 2011; Ventola, 2015). Seeing the danger of resistant bacteria call for new therapy and medicine are issued unfortunately which is rare. (Ahmad et al., 2017; Ayukekbong et al., 2017; Strachan & Davies, 2017).

In developing countries the main reason of antibiotic reason is overuse and inappropriate prescription Internationally. (Ayukekbong et al., 2017). Each year the death percentage for antibiotic resistance is increasing and several millions people are dying. and no scenario of decreasing the rate leads to a most important public health threat worldwide. (Brown et al., 2019; Dramé et al., 2020; Rather et al., 2017).

Soon after 1945, Sir Alexander Fleming upstretched alarm about overusing antibiotic, he warned us about the overuse, even if he was the head behind antibiotic resistance. (*Sir Alexander Fleming - Biographical*, n.d.). The development and distribution of resistant bacteria strains has a straight connection with consumption of antibiotics shown by epidemiology studies. ("The Antibiotic Alarm," 2013a). DNA's are prone to mutation and resistance instinctively occurs because of it. (AF & RJ, 2014) Bacteria takes up genes from relatives or nonrelative bacteria via plasmid and

transforms other bacteria antibiotic resistance.

Chapter 3

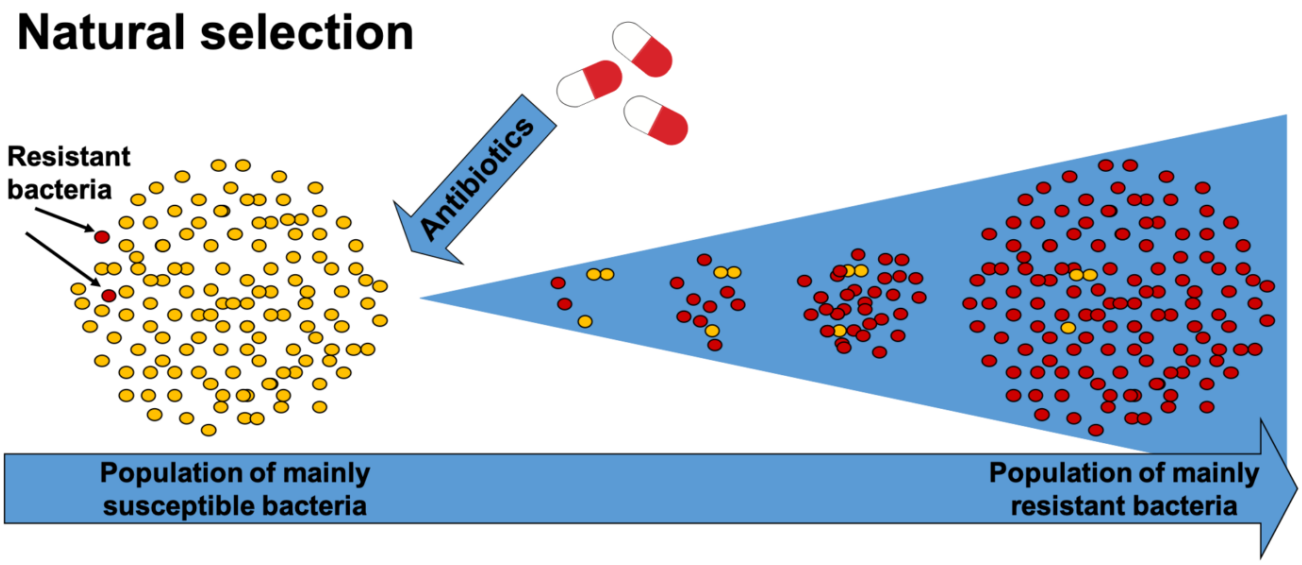
Natural causes

3.1

Mutation:

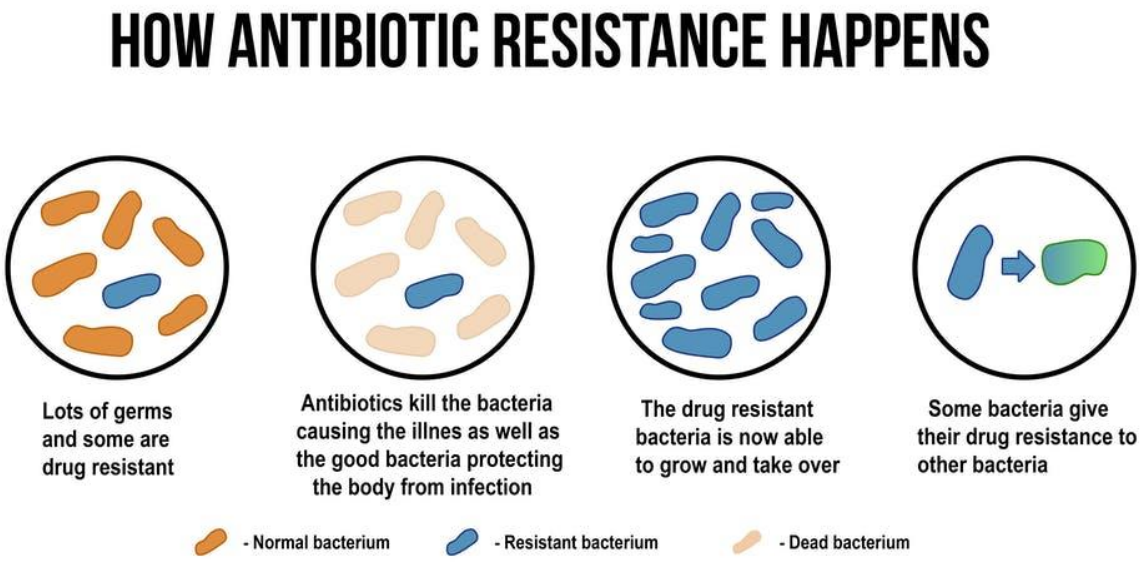
One of the process is to get resistance is via mutations in different chromosomal loci (Aminov & Mackie, 2007). The resistant bacteria needs to reproduce to treat the bacterial population with inspection of specific antibiotic, which are made for them. Increasing number of resistant bacteria and end population with those antibiotic resistant bacteria will be seen. Those bacteria will increase in numbers and in the end population will mainly be resistant bacteria. (*Mutations and Selection – Antibiotic Resistance – ReAct*, n.d.)

Figure 1 Mutation Occurring in bacterial population



In the first phase there is large population mostly consisting the bacteria which are antibiotic susceptible and other bacteria are antibiotic resistance. A bactericidal was added in the population which resulted in survival of resistant bacteria and death of susceptible bacteria. Time went on and the number of resistant bacteria continues to proliferate even in the presence of antibiotic. The last phase is population of resistant bacteria. (*Mutations and Selection – Antibiotic Resistance – ReAct*, n.d.).

Figure 2 Mutation happening in susceptible bacteria



By this figure it can be said that mutation occurs when resistant bacteria are present in large population. For that mutation susceptible bacteria turns into resistant bacteria.

3.2

Mutation rate:

It is very common for mutation rate “in vitro” that in presence of given amount of antibiotic in the population of bacteria mutation is very much noticeable. If it is noted more on the values as number of mutant cell and not event of mutations then there will be one note which is favorable selection for mutation which will lead to antibiotic resistance phenotype (Shapiro, 1997). Perhaps prediction for the development of antibiotic resistance is very much of a work and plays important role. Regarding mutation rate there is a scientific guff about it of antibiotic resistance that it is accessible in a very poor way habitually. The main purpose of mutation rate is to understand the various paths and concept of it and encouraging and predicting the development of mutational resistance to bacteria. (Luria & Delbrück, 1943)

Chapter 4

Horizontal gene transfer

The exchange or taking up of genetic material from one bacterium to another bacteria is the process which is called horizontal gene transfer (HGT). To become resistant for a bacterium the easiest way is to acquire genes from other resistant bacteria.

Genomic sequencing of bacteria enables HGT events to be identified. Huge amount of data can be extracted by sequence based studies, yet it could be limited either to identify genes which are already known or to find out novel sequence which function is known and depends on high homology to known sequence. High number of studies have revealed of previously unknown Antibiotic resistant gene (ARG) present in environments such as soil (Riesenfeld et al., 2004; D'Costa et al., 2006; Allen et al., 2009; Donato et al., 2010; Torres-Cortes et al., 2011; Perron et al., 2015) or activated sludge (Mori et al., 2008; Parsley et al., 2010) as well as in the microbiota of animals (Kazimierczak et al., 2009; Wichmann et al., 2014) and humans (Sommer et al., 2009; Cheng et al., 2012; Moore et al., 2013, 2015; Card et al., 2014; Fouhy et al., 2014; Clemente et al., 2015).

Contribution of the Various HGT Mechanisms to the Spread of ARGs

Conjugation, transformation, phage-mediated transduction, and introgression; these are the four major path for horizontal gene transfer.

4.1

Conjugation:

Conjugation is the process of HGT where straight joining happens between two bacterial cells.

The method requires a bi functional enzyme for separating and rejoining. The bi functional enzyme had trans-esterase activities built into them. By helicase enzyme DNA's unwinding happens also the DNA is carried across the covalent link between the two cells which then will be ready to rejoin into the new bacterium's makeup.

Conjugation has been for various kind of research approaches. It's been noticed that majority of HGT goes for this path smoothly. There have some surveys, and it indicates that most common version of DNA transferred via bacterial conjugation is linked to antibiotic resistance in some way.

4.2

Transformation:

One more common way of HGT for transmitting DNA is transformation. In this method natural way is chosen to complete the process of incorporating DNA into their own genome from another organism. A piece of DNA exits the cell from the bacterial cell and let be taken up by another, nearby bacterium, this process is noticed. It can then be incorporated into its own DNA, which can subsequently be exploited to gain new capabilities.

Cell speciation, adaptability, and cellular evolution are all dependent on this process, as are the other HGT processes. It can aid in the transfer of DNA to another organism in order to promote

virulence and improve metabolic reaction efficiency. Above all, this mechanism has the potential to add a key new defense function: antibiotic resistance.

4.3

Phage-Mediated Transduction:

Bacteriophages (also known as 'phages') are viruses that infect bacterial cells. Temperate bacteriophages are a type of phage capable of transferring DNA from one bacterium to another. Phage-mediated transduction is the name given to this process.

In bacterial cells, phage-mediated transduction has been reported, mainly transmitting genes involved in virulence and antibiotic resistance. In a 2011 study acknowledgment of three kinds of environmental bacteriophages were recognized which were put into two bacterium species: Enterococcus faecalis and *Enterococcus gallinarum*.

The after effect of transduction and exposing bacteria to thousands of microbes it was very much noticeable that most of *Enterococcus fecalis* bacteria had established resistance to tetracycline, whereas the majority of *Enterococcus gallinarum* bacteria had developed resistance to gentamicin. So, it was very obvious that transduction is un doubt ably one of the most way to perform antibiotic resistance.

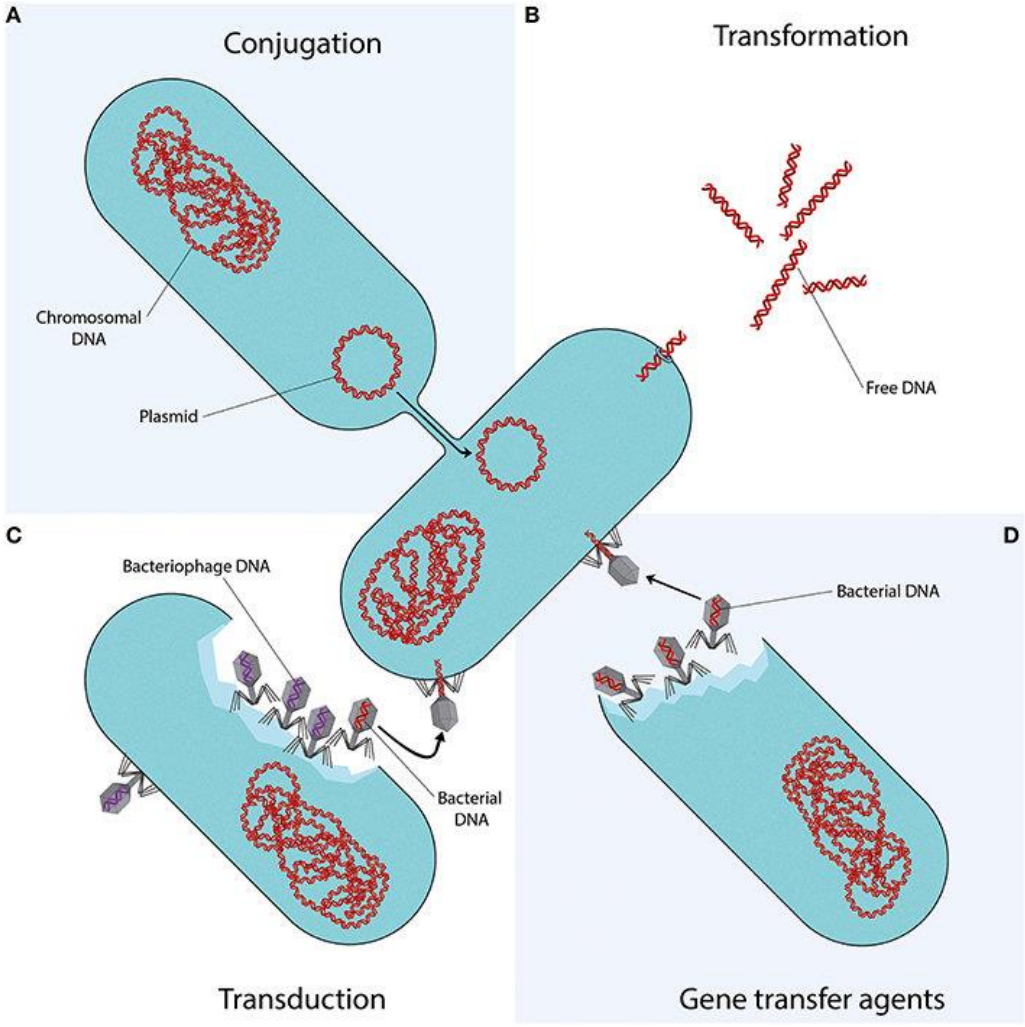
4.4

Introgression:

HGT is one of a kind of method where variety of species participate as well as plants and bacteria. This process of HGT called introgression happens 'back-crossing hybridizing' of one organism with another. For the case of bacteria one species can hybridize with another making a new, 'hybrid' bacteria that has DNA from both of the original organisms.

Many noticeable discoveries have taken place where new hybrid bacteria have expanded antibiotic resistance because ofof this form of DNA hybridization — a trait that none of the original species possessed.(*Horizontal Gene Transfer and Antibiotic Resistance*, n.d.; *Resistance through Horizontal Gene Transfer*, n.d.)

Figure 3 Mechanism of horizontal gene transfer



Chapter 5

Man-made causes of Antibiotic resistance

5.1

Overuse:

Antibiotic usage is obviously driving the emergence of resistance. (Read & Woods, 2014). Antibiotic usage is connected to development and spreading of antibiotic-resistant bacterium strains, according to epidemiological research. *("The Antibiotic Alarm," 2013b)*

The enormous volume of antibiotics given in the United States implies that much work remains to be done to minimize their use.(Gross, 2013). In 2010, 22.0 according to surveys standard units (one dose, i.e., one tablet, capsule, or ampoule) of antibiotics were directed for per person in the United States, according to the IMS Health Midas database, which estimates antibiotic consumption based on the volume of antibiotics sold in retail and hospital pharmacies. (Van Boeckel et al., 2014).

Antibiotics are unregulated in many other nations and are available without a prescription over the counter. (Michael et al., 2014). Antibiotics are freely accessible, plentiful, and inexpensive as a result of the absence of regulation, which encourages abuse. In nations where antibiotics are restricted, the ability to acquire such drugs online has made them more accessible. (Michael et al., 2014).

5.2

Inappropriate Prescribing:

Antibiotics that are given incorrectly contribute to the spread of resistant microorganisms. In 30 percent to 50 percent of cases, the therapeutic indication, agent choice, or duration of antibiotic therapy are wrong, according to studies. (Luyt et al., 2014). In comparison, investigators at the Karolinska Institute in Sweden were able to identify the probable pathogen in 89% of patients with CAP through use of molecular diagnostic techniques (polymerase chain reaction [PCR] and semiquantitative PCR). (Bartlett JG; Gilbert DN; Spellberg B., 2013). Furthermore, it has been discovered that large amount of of antibiotics recommended in intensive care units (ICUs) are unneeded, inappropriate, or suboptimal.(Luyt et al., 2014). Antibiotics given incorrectly have dubious therapeutic value and expose patients to antibiotic-related problems. (Lushniak, 2014). Subinhibitory doses of Antibiotic increases the growth of antibiotic resistance by endorsing genetic modifications such as gene expression changes, HGT, and mutagenesis. (Viswanathan, 2014). Amplified mutagenesis and HGT help antibiotic resistance and propagation, improvement of virulence can happen if changes in antibiotic-induced gene expression happens. (Viswanathan, 2014). In organisms like Pseudomonas aeruginosa, low dosages of antibiotics have been demonstrated to lead to strain diversification. Piperacillin and/or tazobactam at subinhibitory concentrations have also been demonstrated to cause extensive proteome changes in Bacteroides fragilis. (Viswanathan, 2014).

5.3

Broad range Agricultural Use:

Antibiotics are commonly utilized as growth supplements in cattle in both the developed and developing worlds. *("The Antibiotic Alarm," 2013a)*. Antibiotics are utilized in animals to stimulate growth and prevent infection, with an estimated 80 percent of antibiotics sold in the United States going to animals. (Spellberg & Gilbert, 2014). Antimicrobial treatment of livestock is supposed to improve the animals' overall health, resulting in increased yields and a higher-quality output. (Lee Ventola, 2015). Indirectly human consume antibiotics because of usage of it in livestock. When people consume food the unknowingly ingest antibiotic. (Golkar et al., 2014). The transfer of resistant bacteria from farm animals to humans was first documented more than 35 years ago, when significant rates of antibiotic resistance were discovered in both farm animals and farmers' gut flora. (Bartlett et al., 2013). Molecular method detected that lately resistant bacteria comes to human through farm, more precisely when people consume meat. (Bartlett et al., 2013). This occurs as a result of the following events: 1) Antibiotics kill or suppress vulnerable bacteria in food-producing animals, allowing antibiotic-resistant microorganisms to grow; 2) Resistant bacteria are spread through the food supply to humans; 3) these bacteria can cause illnesses in humans, which can lead to serious health problems. Antibiotic use in agriculture has an impact on the microbiome in the environment. (Bartlett et al., 2013). Antibiotics given to livestock are expelled in urine and stool in up to 90% of cases, and then broadly disseminated through fertilizer, groundwater, and surface runoff. (Bartlett et al., 2013). Tetracyclines and streptomycin are also used as insecticides on fruit trees in the western and southern United States. While this application accounts for a much lesser percentage of overall antibiotic use, the geographic dispersion that

results can be significant. (Golkar et al., 2014). This approach also exposes microorganisms in the environment to growth-inhibiting substances, affecting the ecology of the environment by raising the proportion of resistant vs vulnerable bacteria. (Golkar et al., 2014).

Antibacterial products used for hygiene or cleaning purposes may add to the problem by limiting the development of environmental antigen immunities in both children and adults. (Golkar et al., 2014; Ventola, 2015)

Chapter 6

Conclusion

The influencing factors are listed above. Antibiotics' remarkable health advantages are being jeopardized by the rapid emergence of antibiotic-resistant microorganisms.(Golkar et al., 2014). A global crisis, owing to widespread overuse of antibiotics and a shortage of novel antibiotic agents being developed by pharmaceutical companies to talk about the problem.(Bartlett et al., 2013). Now this problem resistance of antibiotic has made us sufferer more than users which has put us in noteworthy financial and health burden on the United States' health-care system and population.(Golkar et al., 2014). Coordinated efforts to enact new regulations, restart research initiatives, and explore crisis-management strategies are critical.(Gould & Bal, 2013)

Chapter 7

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