



ANTIBIOTIC RESISTANCE: CAUSES AND CONSEQUENCES

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ABSTRACT

Antibiotic resistance occurs when bacteria grow and spread in the presence of antibiotics that are normally active against them. The first antibiotic marketed is Penicillin in 1941; soon it got resistance to bacteria. After Penicillin there were several other antibiotics introduced in the market but most of them got resistant to bacteria. The causes of antibiotic resistance are its underuse, overuse, inappropriate use, extensive agriculture use, and lack of regularity in developing countries. Health and economic impacts are two major consequences of antibiotic resistance we need to face at the present moment.

KEYWORDS: Antibiotics, Antibiotic Resistance, Bacteria, Health Impact, Economic Impact.

INTRODUCTION

Antibiotic resistance is the condition in which bacteria changes in response to treatment with the given chemical, commonly known as an antibiotic. As a result, any disease is harder to treat than in the condition with the non-resistant bacteria. According to the United States Center for Disease Control and Prevention (CDC)'s antibiotic resistance report, in the United States only, more than 2.8 million antibiotic-resistant infections occur each year and which results in more than 35,000 people's death.^[1] The CDC states the antibiotic resistance situation as "Antibiotic resistance happens when germs like bacteria and fungi develop the ability to defeat the drugs designed to kill them. That means the germs are

not killed and continue to grow. Infections caused by antibiotic-resistant germs are difficult and sometimes impossible to treat." Hence, there is a challenge, not only to the researchers and pharmaceuticals who involved directly combating it but also to the entire civilization.

Figure 1 depicts how antibiotic resistance happens. There are a lot of germs in our body and few are resistant to antibiotics. When we take antibiotics, it kills bacteria causing illness and they also kill good bacteria protecting the body from infections. After that, antibiotic-resistant bacteria grow and take over, some bacteria give their antibiotic resistance to other bacteria, causing more problems.

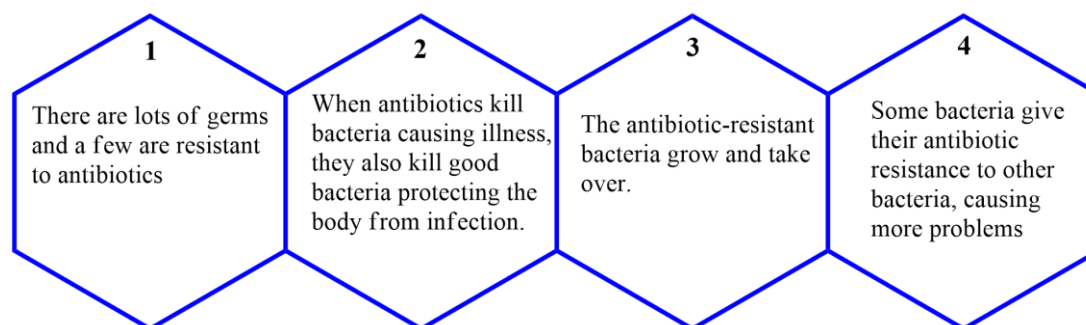


Figure 1: Process of Antibiotic Resistance.^[2]

This world had already suffered from similar situations like tuberculosis, plague pandemic.^[3] It has already been proved that antibiotics were and still are the great benefits but more we are using antibiotics, the more we are on the verge of antibiotic resistance challenges. More

importantly, the unnecessary use of these medicines to treat patients increases the danger of such resistance.

The first discovery of Penicillin in 1928 and its introduction as an antibiotic in 1941,^[4] it has successfully treated soldiers that get injured and ill during World War

II and many more until now. After that, several new antibiotics were introduced in the market, such as Tetracycline, Erythromycin, Methicillin, Gentamicin, Vancomycin, and many more. Over time, these antibiotics became resistant to kill bacteria.

Soon after the discovery of Penicillin, it became resistant to bacteria called *Staphylococcus aureus*, which was identified in 1942. Similarly, antibiotic Vancomycin was

discovered in 1958 and found its resistance with *Enterococcus faecium* in 1988 and *Staphylococcus aureus* in 2002. The antibiotic Amphotericin B was discovered in 1959 and found resistance with *Candida auris* in 2016. Methicillin was discovered in 1960 but unfortunately found its resistance to *Staphylococcus aureus* later in the same decade. Table 1 listed details about the antibiotic released year and resistant germ identified year.

Table 1: Antibiotic Resistance List.^[5]

Antibiotic Approved or Released	Year Released	Resistant Germ Identified	Year Identified
Penicillin	1941	Penicillin-resistant <i>Staphylococcus aureus</i>	1942
		Penicillin-resistant <i>Streptococcus pneumoniae</i>	1967
		Penicillinase-producing <i>Neisseria gonorrhoeae</i>	1976
Vancomycin	1958	Plasmid-mediated vancomycin-resistant <i>Enterococcus faecium</i>	1988
		Vancomycin-resistant <i>Staphylococcus aureus</i>	2002
Amphotericin B	1959	Amphotericin B-resistant <i>Candida auris</i>	2016
Methicillin	1960	Methicillin-resistant <i>Staphylococcus aureus</i>	1960
Extended-spectrum cephalosporins	1980 (Cefotaxime)	Extended-spectrum beta-lactamase-producing <i>Escherichia coli</i>	1983
Azithromycin	1980	Azithromycin-resistant <i>Neisseria gonorrhoeae</i>	2011
Imipenem	1985	<i>Klebsiella pneumoniae</i> carbapenemase (KPC)-producing <i>Klebsiella pneumoniae</i>	1996
Ciprofloxacin	1987	Ciprofloxacin-resistant <i>Neisseria gonorrhoeae</i>	2007
Fluconazole	1990 (FDA approved)	Fluconazole-resistant <i>Candida</i>	1988
Caspofungin	2001	Caspofungin-resistant <i>Candida</i>	2004
Daptomycin	2003	Daptomycin-resistant methicillin-resistant <i>Staphylococcus aureus</i>	2004
Ceftazidime-avibactam	2015	Ceftazidime-avibactam-resistant KPC-producing <i>Klebsiella pneumoniae</i>	2015

Enterococcus spp, *S. aureus*, *K. pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. collectively known as ESKAPE are main resistant bacteria which increasingly involves in infectious diseases in humans. These are listed by world health organization (WHO) as priority antibiotic-resistance bacteria to guide research, discovery, and development of new antibiotics. It is found that these ESKAPE bacteria are transmitted in hospital communities.^[6]

CAUSES

We might have a question of why antibiotics are resistant to microbes and how we human beings are correlated.

Bacteria and viruses are lower ends at their evolution. Their genes mutate faster enough to keep them survive, while the human genes mutate less frequently since they are the most advanced creature in the entire evolution till to date. Unlike in human hosts, in bacteria, the genes can be inherited from relatives and nonrelatives, which allow antibiotic resistance to be transformed from one species to another species of bacteria.^{[7], [8]} The resistance is most commonly associated with extrachromosomal elements such as different types of mobile DNA segments - plasmids, transposons, and integrons from other bacteria in the environment.^[9] The plasmid-mediated transfer of antibiotic resistance is the main focus of investigation because of practical as well as medical significance.^[10]

There are some causes of the antibiotic resistance crisis.^[11]

- Overuse
- Inappropriate prescribing
- Extensive agricultural use
- Unavailability of new antibiotics
- The regulatory barrier to developing new antibiotics
- Increase in international trade and travel

Unlike in developed countries, in developing countries, antibiotics are unregulated and can be found over the counter. Hence its overuse, underuse, and inappropriate use are in high condition. Also, the availability of online purchase of antibiotics in developed countries where its regulation is still challenged, are adding overuse of antibiotics. More importantly, farm animals are given antibiotics as a growth supplement for their growth, disease prevention, larger yields, and higher quality products. Antibiotics are ingested into humans if they consume animal foods that are treated with antibiotics. A large proportion of antibiotics given to farm animals are excreted through their urine and stool and then widely dispersed through fertilizers, groundwater, and surface runoff, which results in the growth of resistance versus susceptible microorganisms in the environments.^[12]

Van Boeckel *et al.*^[13] were analyzed pathogens to find out the resistance in animals in developing countries. China and India were found largest hotspots of the resistance. It was found that from 2008 to 2018 the proportion of antimicrobials showing resistance over 50% has increased from 0.13 to 0.34 in pigs and from 0.15 to 0.41 in chickens

Antibiotics like fruits-pesticides also contribute to the environmental growth of resistant microorganisms. Antibacterial hygiene and cleaning products also contribute to the inability of the development of environmental immunities in children and adults, which compromise the immune system. Also, the large number of major pharmaceutical companies abandoned antibiotic research as there is a lack of profit because antibiotics are used in a relatively short period and are curable, unlike other chronic diseases; also contribute to the lack of opportunity to treat antibiotic resistance.

CONSEQUENCES

Severe infections, complications, longer hospital stay, and increased mortality are the primary consequences of antibiotic resistance.^[14] Impact of antibiotic resistance can be divided into two major parts-health and economic consequences

Health Consequence

As a consequence of antibiotic resistance, infected people cannot get adequate treatment by available antibiotics. Antibiotic resistance cause additional infections, it is found that additional infections result not due to susceptible strains but due to resistant strains.^[15] The antibiotic resistance increases the risk of safety and efficacy of surgical procedure which limits available and often lifesaving treatment options.^[16] Administration of effective therapy is often delayed by antibiotic resistance. The most significant factor for delaying effective therapy is the mismatch between empirical therapy and subsequent antibiotic susceptibility test results.^[17] Table 2 summarizes problems, examples, and consequences of antibiotic resistance.

Table 2: Examples of the consequences of antibiotic resistance.^[16]

Problem	Example	Consequences
Infections caused by MDR bacteria	ESBL <i>Escherichia coli</i> bacteraemia treated empirically with ceftriaxone Carbapenem-resistant <i>Acinetobacter baumannii</i> infection Infection with colistin-resistant <i>A. baumannii</i>	Inadequate therapy/delay in effective therapy Less efficacious or more toxic agents Infection with limited or no therapeutic options
Colonization with MDR bacteria	Failure of fluoroquinolone prophylaxis to prevent infection by resistant strains of <i>E. coli</i> after transrectal ultrasound-guided prostate biopsy	Additional infections
Infections caused by non-MDR bacteria	Vancomycin for MSSA Piperacillin/tazobactam empiric treatment for neutropenic sepsis where the causative organism is MSSA	Less efficacious treatment Excessively broad-spectrum treatment
Hospitalization	The spread of epidemic/virulent VRE clones in a unit Outbreak of carbapenem-resistant <i>Klebsiella</i> spp. in a unit	Additional infections Lack of access to optimal or lifesaving procedures Lack of access to optimal or lifesaving procedures

Abbreviations: ESBL, extended-spectrum β -lactamase; MDR, multidrug-resistant; MSSA, methicillin-susceptible *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*

Economic Consequence

It is estimated that the cost of antimicrobial resistance is \$55 billion (\$20 billion for health care and about \$30 billion in productivity) per year in the United States.^[18] It is reported that the hospital will spend an additional \$10,000 to \$40,000 to treat a patient infected with resistant bacteria.^[19] The healthcare costs, length of stay

in hospitals, morbidity, and mortality are increases by antibiotic resistance in both developed and developing countries. McGrown Jr.^[20] pointed out "The net economic impact of resistance can be viewed as the attributable cost of treatment of infection due to resistant isolate ("treatment cost") minus the cost of preventing such infections ("prevention cost")".

Table 3: The perspective of the economic impact of antimicrobial-resistance.^[20]

	Focus	Outcome	Time	Motivation	Approach
Physician	Individual	Health	Short	Professionalism	Treatment
Patient	Individual	Health	Short	Health	Treatment
Provider	Care Group	Lower cost	Short	Profit	Cost containment
Industry	Clients	Sales	Short, long	Profit	New drugs, viable old drugs
Public	Population	Health	Long	Social good	Lower chance of resistance

Table 3 summarizes the perspective of the economic impact of antimicrobial-resistance among physicians, patients, health care providers, pharmaceutical industry, and public. For example, both physician and patient have the same focus, outcome, time, and approach but only differ in motivation, the former is motivated through professionalism while later is motivated for better health. Comparison of each group can be done from the given Table 3.

CONCLUSION

Different initiatives need to be taken from every corner to prevent antibiotic resistance. Prudent use of antibiotics, reducing unnecessary agricultural use, more investment in the development of new antibiotics research. In developed countries, millions of people are affected, and thousands are died each year because of antibiotic resistance. Amid the impoverished condition of medical facilities, the chance of drug resistance is very high in developing countries too. So, the crisis arising from antibiotic resistance is real, and we all need to be wise and responsible during the use of antibiotics.

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