# What is Antibiotic Resistance and Why is it a Problem?

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## Abstract

Antibiotics are agents that fight infections. Although there are many microorganisms, fungi, viruses, parasites, for which there are agents used to treat infections caused by them, we often reserve the term antibiotic to refer to agents used against bacteria. Used properly, antibiotics can save lives. But there is a growing problem of antibiotic resistance. It happens when bacteria change, through mutations, and become able to resist the effects of an antibiotic or the susceptible organisms are replaced by organisms naturally resistant to the antibiotic. These resistant organisms can spread to other people. They can also cause infections that other antibiotics cannot cure. Methicillin-resistant *Staphylococcus aureus* (MRSA) is one example. It can cause infections that are resistant to a number of commonly used antibiotics. This article will discuss how resistance occurs, problems caused by resistant organisms and how to avoid increasing the spread of resistant isolates of organisms.

*Keywords:* antibiotic, microorganism, microbe, resistance, synthetic, semisynthetic, penicillin

## Introduction

Why and how do microbes become resistant to antibiotics? Why are antibiotics made in nature to begin with? Let's address these and other questions about antibiotics in somewhat less technical terms. First, we should define several terms we will use throughout the article. We will use the terms susceptible or non-susceptible rather than sensitive and non-sensitive to describe the ability/inability of antibiotics to work against bacteria. Sensitivity tends to mean too many things including an allergy to something such as an antibiotic. Another term that is often used generically is antibiotic. In a technical sense, antibiotics are chemicals that are produced by a microorganism. That is, all or part of the chemical structure is produced by a microorganism.

For example, penicillin is produced by a mold called *Penicillium*. There are semisynthetic antibiotics (such as semisynthetic penicillins) that are partially produced by organic synthesis in the pharmaceutical laboratory, but the base structure is still produced by a microorganism.

Why? Because the microorganism is far more efficient at making the antibiotic's backbone structure, such as the 6-aminopenicillanic acid or 6 APA for penicillins. Antimicrobials such as sulfa drugs are not technically antibiotics but rather chemicals synthesized in the pharmaceutical laboratory that are not made in any way by microbes. They are simply antimicrobials and sometimes referred to as systemic antiseptics. For this article we will use antibiotic in a general way because our discussion covers both true antibiotics and systemic antimicrobials.

## Why Are There Antibiotics?

The term "antibiotic" was first used by Selman Waksman in 1941. It is well known that most naturally occurring antibiotics are produced by soil microorganisms. Indeed, for many years drug companies searched for new antibiotics by trying to isolate organisms producing antibiotics from soil samples obtained from all over the world. It would appear that soil organisms evolved to produce antibiotics to decrease competition for nutrients in their environment. The susceptible competition would be inhibited or killed off and the antibiotic-producing organism would colonize without competition. A logical question then becomes why are the antibiotic-producing organisms not killed by their own antibiotic? Sometimes they are but other times these organisms are resistant to the antibiotic. This article will discuss the naturally occurring process of antibiotic resistance, which has become so important in medicine today.

## Antibiotic Resistance in General Terms

In the human environment antimicrobial resistance (ABR) is the ability of a microbe to resist the effects of medication previously used to treat them (WHO, 2016). This broad term (ABR) is usually used to indicate antibiotic resistance, which applies to bacteria and antibiotics. A person cannot become resistant to antibiotics. Resistance is a property of the microbe, not a person or other organism infected by a microbe (CDC 2015a).

Resistance arises through one of the following ways: natural resistance in certain types of bacteria; genetic mutation; or by one species acquiring resistance from another (Alliance for Prudent Use of Antibiotics, 2014). Resistance can appear spontaneously because of random mutations; or more commonly, following gradual buildup over time primarily because of misuse of antibiotics or antimicrobials (CDC, 2015b). As mentioned, these processes are all naturally occurring. A number of these resistance processes will be discussed in this article. Resistant microbes are increasingly difficult to treat, requiring alternative medications or higher doses—which may be more costly and/or more toxic. Microbes resistant to multiple antimicrobials are called multidrug resistant (MDR); or sometimes the bacteria are referred to as superbugs (CDC, 2015b). Antimicrobial resistance is on the rise with millions of deaths every year worldwide (WHO, 2015). A few infections are now completely untreatable with antibiotics because of resistance. All classes of microbes develop resistance (fungi, antifungal resistance; viruses, antiviral resistance; protozoa, antiprotozoal resistance; bacteria, antibiotic resistance).

## Antibiotic Misuse

Antibiotics should only be used when needed as prescribed by health professionals (CDC, 2015a). The prescriber should adhere to these guidelines or "rights": the right patient, the right

drug, the right dose, the right route, and the right time (Federico, 2016). Narrow-spectrum antibiotics should be preferred over broad-spectrum antibiotics. Narrow spectrum antibiotics better target specific organisms and are less likely to induce resistance (Health News and Evidence, 2013). Cultures should be taken before treatment when indicated and treatment potentially changed based on the susceptibility report (CDC, 2014). For people who take these medications at home, education about proper use is essential. Health care providers can minimize spread of resistant infections by use of proper sanitation: including handwashing and disinfecting between patients; and should encourage the same of the patient, visitors, and family members (CDC, 2014).

Rising drug resistance can be attributed to three causes: use of antibiotics in the human population; in the animal population; and spread of resistant strains between humans or non-human sources (CDC, 2015b). Antibiotics increase selective pressure in bacterial populations, causing vulnerable bacteria to be unable to compete for growth substances and thus die off—this increases the percentage of resistant bacteria which continue growing.

With resistance to antibiotics becoming more common there is greater need for alternative treatments. Calls for new antibiotic therapies have been issued, but new drug-development is very slow (Cassir, N., Rolain, J., & Brouqui, P., 2014). Unfortunately, the costs of developing new antibiotics exceeds the financial gain perceived by pharmaceutical companies. Examples of drug-resistant bacteria include: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus* (VRSA), extended spectrum beta-lactamase (ESBL), vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant *A. baumannii* (MRAB) (CDC, 2016a). A World Health Organization (WHO, 2014)) report released April 2014 stated, "... this serious threat is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country. Antibiotic resistance is now a major threat to public health (WHO, 2014)." According to the Centers for Disease Control and Prevention: "Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections (CDC, 2016b)."

## Evolution and Spread of Antibiotic Resistance and Some History

In 1926, Alexander Fleming discovered penicillin, a substance that appeared able to inhibit bacterial growth of many kinds of bacteria. In 1939, Edward Chain and Howard Florey further studied penicillin and later carried out trials of penicillin on humans with what were considered fatal bacterial infections. Fleming, Florey and Chain shared the Nobel Prize in 1945 for their work, which ushered in the era of antibiotics. Interestingly, earliest traces of antibiotic use date back thousands of years. Tetracycline has been found in skeletons from Sudanese Nubia, an area that included ancient Egypt (Pollock, M.R., 1967). Researchers believe that ancient Nubians were actually brewing tetracycline into their beer or otherwise incorporating it into their diets over a long period of time because the compound was found embedded deep in their bones and the population's documented infectious diseases seem to be quite low. This discovery overturned the commonly-held belief that antibiotics didn't exist before 1926. Bacteria with resistance to antibiotics predate medical use of antibiotics by humans. In 1962 the presence of penicillinase was detected in dormant endospores of Bacillus licheniformis, a common soil organism with

commercial uses, that were revived from dried soil preserved since 1689 in the British Museum (Pollock, M.R., 1967).

In 2016, WHO (WHO, 2016) indicated the following reasons for the widespread use of antibiotics:

1. increasing global availability over time since the 1950s
2. uncontrolled sale in many low- or middle- income countries, where they can be obtained over the counter without a prescription, potentially resulting in antibiotics being used when not indicated. This may result in emergence of resistance in any remaining microorganisms
3. use in cattle and other livestock. This is a major factor in the spread of antibiotic resistance.

Antibiotic use in livestock feed at low doses for growth promotion is an accepted practice in many industrialized countries and is known to lead to increased levels of resistance (Mathew, A.G., Cissell, R., & Liamthong, S., 2007). Releasing large quantities of antibiotics into the environment during pharmaceutical manufacturing through inadequate wastewater treatment increases the risk that antibiotic-resistant strains will develop and spread (Larsson, D.G. and Fick, J., 2009). It is uncertain whether antibacterials in soaps and other products contribute to antibiotic resistance, but they are discouraged for other reasons (Aiello, A.E., Larson, E.L. & Levy, S.B, 2007).

Increasing bacterial resistance is linked with the volume of antibiotic prescribed, as well as missing doses when taking antibiotics (McNulty, C.A.M., Boyle, P., Nichols, T., Clappison, P. & Davey, P., 2007). Inappropriate prescribing of antibiotics has been attributed to a number of causes, including people insisting on antibiotics, physicians prescribing them as they feel they do not have time to explain why they are not necessary, and physicians not knowing when to prescribe antibiotics or being overly cautious for medical and/or legal reasons.

Up to half of antibiotics used in humans are unnecessary and inappropriate. For example, a third of people believe that antibiotics are effective for the common cold , and the common cold is the most common reason antibiotics are prescribed even though antibiotics are not effective against viruses (McNulty, C.A.M., Boyle, P., Nichols, T., Clappison, P. & Davey, P., 2007). A single regimen of antibiotics even in compliant individuals leads to a greater risk of resistant organisms to that antibiotic in the person for a month to possibly a year after use of the antibiotic (Costelloe, C., Metcalfe, C., Lovering, A., Mant, D. & Hay, A.D., 2010).

In summary, it is the organism that mutates to become resistant to an antibiotic. This is naturally occurring and does not require the antibiotic to be present. The resistant organism is present in small numbers but usually does not compete well with the "normal" susceptible bacteria. However, our use of antibiotics can kill off the susceptible bacteria, allowing the resistant isolates to become the predominant flora.

Certain antibiotic classes screen for resistance more than others. Increased rates of MRSA infections are seen when using glycopeptides, cephalosporins, and quinolones (Muto, C.A. et al., 2003). Cephalosporins, and particularly quinolones and clindamycin, are more likely to produce colonization with *Clostridium difficile* (Thomas, J.K., et al. 1998).

Factors within the intensive care unit setting such as mechanical ventilation and multiple underlying diseases also appear to contribute to bacterial resistance (Thomas, J.K. et al., 1998). Poor hand hygiene by hospital staff has been associated with the spread of resistant organisms (Girou,E. et al., 2006), and an increase in hand washing compliance results in decreased rates of all bacteria (Swobota, S.M., et al., 2004).

Improper use of antibiotics can often be attributed to the presence of structural violence such as civil war in particular regions. Socioeconomic factors such as race and poverty affect accessibility of and adherence to drug therapy. The efficacy of treatment programs for drug-resistant strains depends on whether or not programmatic improvements take into account the effects of structural violence.

## Mechanisms – A Brief Discussion

The five main mechanisms by which microorganisms exhibit resistance to antimicrobials are (Munita, J.M., & Arias, C.A., 2016):

1. Drug inactivation or modification: for example, enzymatic deactivation of *penicillin G* in some penicillin-resistant bacteria through the production of β-lactamases. Most commonly, the protective enzymes produced by the bacterial cell will add an acetyl or phosphate group to a specific site on the antibiotic, which will reduce or destroy the antibiotic's ability to inhibit cell wall synthesis.

2. Alteration of target site, for example alteration of penicillin binding proteins (PBPs)—the binding target sites of penicillins—in MRSA and other penicillin-resistant bacteria.

3. Another protective mechanism found among bacterial species is ribosomal protection proteins. These proteins protect the bacterial cell from antibiotics that target the cell's ribosomes to inhibit protein synthesis. The mechanism involves the binding of the ribosomal protection proteins to the ribosomes of the bacterial cell, which in turn changes its conformational shape. This allows the ribosomes to continue synthesizing proteins essential to the cell while preventing antibiotics from binding to the ribosome to inhibit protein synthesis.

4. Alteration of metabolic pathways, for example some sulfonamide-resistant bacteria do not require para-aminobenzoic acid (PABA), an important precursor for the synthesis of folic acid and nucleic acids in bacteria inhibited by sulfonamides. Bacteria will turn to using preformed folic acid found in host cells.

5. Reduced drug accumulation, by decreasing drug permeability or increasing active efflux (pumping out) of the drugs across the cell surface. These specialized pumps can be found within the cellular membrane of certain bacterial species and are used to pump antibiotics out of the cell before they are able to do any damage. These efflux pumps are often activated by a specific substrate associated with an antibiotic.

## Further Information on Resistance

Antibiotic resistance can be a result of horizontal gene transfer, and also of unlinked point mutations in the pathogen genome at a rate of about 1 in 108 per chromosomal replication

(Levin, B.R., Perrot, V., & Walker, N., 2000). Mutations are rare but the fact that bacteria reproduce at such a high rate allows for the effect to be significant. A mutation may produce a change in the binding site of the antibiotic, which may allow the site to continue proper functioning in the presence of the antibiotic or prevent the binding of the antibiotic to the site altogether. Research has shown the bacterial protein LexA may play a key role in the acquisition of bacterial mutations giving resistance to quinolones and rifampicin. DNA damage induces the SOS gene repressor LexA to undergo autoproteolytic activity (Levin, B.R., Perrot, V., & Walker, N., 2000). This includes the transcription of genes encoding Pol II, Pol IV, and Pol V, which are three DNA polymerases that are required for mutations in response to DNA damage. The antibiotic action against the pathogen can be seen as an environmental pressure. As indicated above, those bacteria with a mutation that allows them to survive, live to reproduce. They then pass this trait to their offspring, which leads to the evolution of a fully resistant colony. Although these chromosomal mutations may seem to benefit the bacteria by providing antibiotic resistance, they also confer a cost of fitness. For example, a ribosomal mutation may protect a bacterial cell by changing the binding site of an antibiotic but it may also slow the process of protein synthesis. Additionally, a study by Levin, B.R., Perrot, V., and Walker, N. (2000), specifically compared the overall fitness of antibiotic resistant strains of *Escherichia coli and Salmonella typhimurium* to drug-sensitive isolates . They observed a reduced overall fitness in the antibiotic resistant strains, especially in growth rate (Levin, B.R., Perrot, V. & Walker, N., 2000).

There are three known mechanisms of fluoroquinolone resistance. Some types of efflux pumps (pump the antibiotic out) can act to decrease intracellular quinolone concentration. In Gram-negative bacteria, plasmid-mediated resistance genes produce proteins that can bind to DNA gyrase, protecting it from the action of quinolones. Finally, mutations at key sites in DNA gyrase or topoisomerase IV can decrease their binding affinity to quinolones, decreasing the drug's effectiveness (Robicsek, A., Jacoby, G.A., & Hooper, D.C 2006).

Antibiotic resistance can also be introduced artificially into a microorganism through laboratory protocols, sometimes used as a selectable marker to examine the mechanisms of gene transfer or to identify individual bacteria that absorbed a piece of DNA that included the resistance gene and another gene of interest. A recent study demonstrated that the extent of horizontal gene transfer among *Staphylococcus* is much greater than previously expected—and encompasses genes with function beyond antibiotic resistance and virulence gene elements(Cheong, X.C. , Beiko, R.G., & Ragan, M.A., 2011).

For a long-time it has been thought that for a microorganism to become resistant to an antibiotic, it must be in a large population. However, recent findings show that there is no necessity of large populations of bacteria for the appearance of antibiotic resistance. We know now that small populations of *E. coli* in an antibiotic gradient can become resistant. Any heterogeneous environment with respect to nutrient and antibiotic gradients may facilitate the development of antibiotic resistance in small bacterial populations and this is also true for the human body. Researchers hypothesize that the mechanism of resistance development is based on four SNP (single-nucleotide polymorphism) mutations in the genome of *E. coli* produced by the gradient of antibiotic. These mutations confer the bacterial emergence of antibiotic resistance (Cheong, X.C., Beiko, R.G., & Ragan, M.A., 2011).

## Recent Antibiotic Resistance Research

Scientists at the Walter Reed Army Institute of Research (WRAIR) have performed extensive research concerning antibiotic resistance at the Multidrug-resistant Organism Repository and Surveillance Network (MRSN) in Silver Spring, MD. The MRSN is responsible for tracking antibiotic resistant organisms in military healthcare facilities throughout the world. Additionally, other organizations such asthe VA and other agencies, rely on the MRSN to track and identify resistant organisms in their facilities. Further, the MRSN re-identifies the isolates and determines through the latest techniques the specific resistance factor(s) involved. Much research has been provided by this group of researchers.

Researchers at WRAIR recently determined the presence of *mrc-1* and $bla_{ctx\text{-}m}$ on a novel IncF plasmid in *E. coli*. This was the first report of the *mcr-1* in the U.S. The mcr-1 gene was first seen in China. This plasmid gene is responsible for colistin resistance. Its insertion into an Enterobacteriaceae organism already possessing other resistance factors is very concerning because colistin is a last-resort antibiotic against some Enterobacteriaceae (McGann, et al, 2016). In another study, WRAIR researchers collaborated to assess another Gram negative organism, *Acinetobacter baumannii*, with New Delhi Metallo- β-lactamase that induces resistance to carbapenem (Waterman, P.E., et al. 2013). These studies, and others, have advanced our knowledge of antibiotic resistance.

Although the process is currently slow, new antimicrobials are being developed. New treatment methods are also being researched such as the use of bacteriophage (bacterial viruses) to inhibit bacteria in wound infections without harming the human host. If we use caution and follow usage guidelines we may curtail the spread of antibiotic resistance.

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