What Factors Contribute to the Modern Spike in Antibiotic Resistant Bacteria, and How Can These Factors Be Controlled?

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Abstract

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There continues to be a rise in antibiotic resistant bacteria. The factors that contribute to this rise and how the factors can be controlled were investigated. The factors researched are included in the following: overuse of antibiotics and antimicrobial agents, lack of bacteria competition, failure to eliminate the diseases, and exchange of genetic material. The investigation concluded the main factor contributing to antibiotic resistant bacteria was the widespread use of antibiotics which in turn affected all other factors identified. The investigation also yielded a variety of solutions that may combat the main factor as well as minor ones, so the emergence of new resistant strains was inhibited and current strains could be controlled effectively. Results show the efficacy of the solutions relies heavily on the widespread involvement and communication between healthcare systems and governments.
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Section 1: Introduction

Before 1928 almost any bacterial infection had the potential to be life threatening, and survival and recovery relied solely on one's immune system and ability to persevere through a series of debilitating symptoms before successfully recovering or eventually succumbing to the disease. Only very recently have antibiotics entered the field of medicine, promising recovery and boosting longevity among the human population. Over time new antibiotics were developed and were able to combat nearly all bacterial infections with efficacy and rendered many serious diseases harmless. Antibiotics were a miracle drug that helped push diseases such as Diphtheria and Scarlet Fever into near extinction from countries with systems of institutionalized medicine (HowStuffWorks, "12 Deadly Diseases...", (n.d)). However, institutionalized medicine and easy access to pharmaceuticals isn't always beneficial. In the United States, the average citizen receives 12.3 prescriptions a year (Retail Prescription Drugs Filled at Pharmacies, (n.d)). The widespread usage and success of antibiotics in combating bacterial diseases made it commonplace. This inevitably would lead to the development of some bacteria achieving resistance through evolution due to constant exposure to the antibiotics and ideal environments for growth and reproduction. Even though antibiotic resistance is on the rise, the prescription of antibiotics is still a fairly frequent practice among doctors. Many different factors are in play when a bacteria achieves resistance. What are these factors and how may we control them? There is a growing health crisis and without ample precautions, the progress made with modern antibiotics could be reversed to a time where a simple infection has the potential to kill.
Section 2: Explanation of Terms:

Antibiotic: An antibiotic is a chemical that either kills or inhibits the multiplication of a bacteria. The class of antibiotics that kills bacteria directly is called *bactericidal*, and antibiotics that inhibit bacterial growth and replication are called *bacteriostatic*. Each antibiotic has a spectrum of bacteria in which it is effective. Antibiotics can either be *broad-spectrum* meaning they are effective in treating many ranges of bacteria or *narrow-spectrum* meaning they are only effective against a narrow range of bacteria. There are many different types of antibiotics that differ in origin, means of inhibiting bacterial growth, and toxicity levels (Antibiotics: Types and Side Effects (n.d)).

Antibiotic Resistance: Resistance is achieved when a bacteria is no longer affected by an antibiotic due to evolution or a change in the bacterial cell's structure rendering the antibiotic useless (Purdom, 2014).

Section 3: A Brief History of Antibiotics and Antibiotic Resistant Strains of Bacteria

The first antibiotic, penicillin, was discovered in 1928 by bacteriologist Alexander Fleming. Penicillin is excreted by the mold species *Penicillium* and causes nearby bacteria colonies to lyse (destruction of cell membrane) themselves effectively killing all bacteria near the mold colonies. This discovery led to the research of antibiotics, but it wasn't until 1938 that H. W. Florey and E. Chain were able to purify penicillin to a stable compound that could be used in the treatment of bacterial infections (History of the development of antibiotics, 2007). The drug was highly successful and further research began for other antibiotic chemicals. This research yielded many different penicillin compounds, each with a different side chain that gave the compound a different effect which led to the development of antibiotics that could be taken
orally and did not break apart in the low P.H. levels of the stomach (History of the development of antibiotics, 2007). Additionally, other antibiotics were discovered such as streptomycin and tetracycline which offered a broad range of efficacy.

With the discovery of penicillin in 1928, the first bacteria with a resistance to penicillin was identified in 1947; this was four years after penicillin began being mass produced. As antibiotics became widespread and commonplace, the bacteria the antibiotics were targeting was able to acquaint itself to types of antibiotics that were commonly prescribed and develop a biological resistance to the chemicals declaring them useless (Antibiotic resistance, (n.d.)). By the 1950s penicillin resistant bacteria was fairly common in hospitals, and the antibiotic methicillin was introduced to fight these newly resistant bacteria (Superbug, super-fast evolution, (n.d.)) . Recently, the number of cases in which antibiotic resistant bacteria has been involved has become more and more common. The "The New York Times" states that there are 32 cases of antibiotic resistant bacterial infections for every 100,000 people (Sack, 2007). A majority of these antibiotic resistant strains originate in the United States and other countries with well-developed healthcare systems.

Section 4: Mechanisms of Resistance and How Bacteria Achieve Resistance

Antibiotics target a bacterial cell's necessary functions such as protein synthesis, reproduction, RNA and DNA synthesis, and disrupting the cell wall. Bacteria can adapt to resist antibiotics that target these vital systems by altering their cellular membrane, so antibiotics cannot diffuse across them. The bacteria do this by limiting the channels in the membrane that the drug can enter. Bacteria can also resist antibiotics by identifying the compound and pumping it out of the cell before it affects the cell. Another mechanism bacterial cells employ is they alter
the molecular structure of the target molecule through genetic mutation, so the antibiotic can no longer bond to its target and is thereby rendered useless. Lastly, bacterial cells can evolve, so they can destroy the antibiotic by deactivating the compound. For example, MRSA (methicillin-resistant \textit{Staphylococcus aureus}) does this by producing beta-lactamase which destroys antibiotic compounds. Bacteria obtains these genes through mutation, exchange of genetic material through plasmid exchange, and by obtaining genetic information from other dead bacteria (Purdom, G., 2014).

\textbf{Section 5: Factors related to Increase in Antibiotic Resistant Strains}

Over the past ten years, the number of cases of antibiotic resistant strains of bacteria has greatly increased. One such is example is methicillin-resistant \textit{Staphylococcus aureus} (Diseases/Pathogens Associated with Antimicrobial Resistance, 2014). According to an experiment done by the American Society for Microbiology, The proportion of MRSA (methicillin-resistant \textit{Staphylococcus aureus}) has increased in U.S. hospitals from less than 5\% in the 1980s to 29\% in 1991 (Lee, B., et al., 2012). Another source claims the number of MRSA cases has doubled in academic hospitals between 2003 and 2008 (MRSA cases, 2012). These numbers are concerning to the Center for Disease Control and epidemiologists, and several factors have been identified explaining the recent increase in antibiotic resistant bugs.

\textbf{Overuse of Antibiotics}

Bacteria are living organisms, and like most other living organisms, they will tend to evolve to survive. The constant exposure of bacteria to broad-spectrum antibiotics will give the bacteria the ability to adapt to the new threat. Once resistant, the strain may continue to spread among individuals of a population.
One reason for the increase in resistant strains of bacteria is that doctors sometimes will prescribe antibiotics to treat even a minor bacterial infection that could be easily dealt with by the patient's immune system over the course of time. According to the CDC 4 out of every 5 Americans are prescribed antibiotics as least once a year (CDC: 4 out of 5 Americans prescribed antibiotics, 2013). This unnecessary use of antibiotics is one of the main causes to the recent rise in antibiotic resistant bacteria. Additionally, antibiotics are also used on an industrial scale in agriculture and animal husbandry to promote healthy crops and livestock (Antibiotics on Farms, 2014). With the widespread use of antibiotic and anti-microbial chemicals, it is inevitable that antibiotic and antimicrobial compounds will be present in landfills, waste water, and the immediate vicinity in which they are used (Drugs in Drinking Water, (n.d)). This wide-spread application is ideal for breeding antibiotic resistant strains since the antibiotics are present everywhere allowing bacteria to adapt.

Natural Selection and Resource Abundance

Natural Selection also plays a key role in the emergence of antibiotic resistant bacteria. Many resistant antibiotic resistant strains of bacteria emerge in hospitals and healthcare facilities where sterile environments are plentiful. The sterility of the facility limits competition among bacteria by killing weaker bacteria and leaving the tougher ones alive through natural selection. The removal of the competing weaker bacteria allows the resistant and stronger bacteria to have access to an excess of resources allowing for the bacteria to thrive and reproduce quickly (Allott A., 2014). The main reason in which bacteria can survive in these harsh sterile environment is the ability of bacteria to form biofilms. These films are made of polymers secreted by aggregates of microbes, fungi, and other bacteria that form a large coating or film that forms to help protect the bacteria from the stress of their environment. Biofilms are extremely difficult for antibiotics
and common antiseptics to kill. This polymer-like structure can form on living and non-living surfaces and is extremely hard to remove since the film provides a penetration barrier that protects the microbes from bactericides (Biofilms on Environmental Surfaces, 2012). If these aggregates are composed of harmful bacteria, it can be extremely difficult to kill and is hazardous to susceptible living things near it. Biofilms are common in hospital settings and are often a cause of infection that is received during a prolonged hospital stay.

The lack of competition allows the tougher and more resistant strains to spread throughout the facility and ultimately increase the number of infections by resistant strains. The larger consequence is these breeding grounds for superbugs spread the resistant strains through infected patients who leave the facility or through other means. Once the bacteria has escaped the medical setting, it is free to spread causing further infections over a large area.

Failure to Complete Prescription Duration

Another instance that contributes to the formation of antibiotic resistant bacteria is that patients sometimes fail to completely eliminate a bacterial infection from their bodies by failing to complete the required amount of antibiotics over a prescribed period of time. This failure to eliminate the infection completely allows some of the remaining bacteria to have a higher tendency to develop resistance to the antibiotic since they were exposed to the drug but not eliminated by it. People sometimes tend to keep any leftover antibiotics in case they feel run down, so they can recover quickly if they catch something again. This can also contribute to the rise of antibiotic resistant bacteria if the leftover antibiotics are not the correct spectrum or strength to kill the current illness (Bernstein, L., 2014).
Plasmid Expression

Once the superbugs are free to interact with other bacteria, antibiotic resistance can be acquired by other bacteria through plasmid expression in which resistant bacteria cells will exchange DNA and genetic information that enables antibiotic resistance. A plasmid is a mobile bundle of DNA that is copied and exchanged between different species of bacteria. New genetic information may eventually be integrated into the chromosomes of the recipient cell. This allows strains to achieve resistance immediately and possibly spread the genetic trait to even more bacteria causing widespread antibiotic resistance (Superbug, super-fast evolution, (n.d)). According to the article "Strain-Specific Transfer of Antibiotic Resistance from an Environmental Plasmid to Foodborne Pathogens", infected patients harbor large amounts of donor and acceptor bacteria allowing for further spread of resistance to other bacteria. The other statement this article makes is plasmids could be exchanged from environmental bacteria located in agriculture, water treatment centers, and healthcare environments to possible life threatening pathogens responsible for illness (Meervenne, et al., 2012). This exchange of genetic information is especially dangerous since it allows for several types of bacteria to gain resistance quickly and further spread the trait to other bacteria causing an overall increase in bacterial antibiotic resistance (McConnell, 1999).

Lack of Antibiotic Variation

No new types of antibiotics have been introduced since the 1980s, and overuse of the ones currently used today is leading to a buildup of resistant bacteria. Without cycling between antibiotics, bacteria will adjust and evolve to develop multiple resistances (Allott, A., 2014). The constant exposure of bacteria to one antibiotic will greatly increase the possibility of resistance.
As seen with penicillin, resistant strains emerged relatively quickly after mass application of penicillin. Without newer ways to treat bacterial infections, it is possible that resistance will catch up with the latest and strongest antibiotics and will no longer be able to be stopped without the introduction of new technology and medicine.

Section 6: Factor Relationships and Severity

A majority of the factors involved in the increase of antibiotic resistant bacteria involve the exposure of bacteria to common antibiotics over extended periods of time allowing for the bacteria to adjust to the active chemical in the antibiotic. Many factors depend on each other to occur. For example, the resistant bacteria that emerge in healthcare facilities are directly related to the overuse of antibiotics and bactericide, but their initial survival may be to the formation of impregnable biofilms and decrease in bacterial competition and are themselves resistant to antibiotics. This lack of competition leads to a buildup of antibiotic resistant bacteria in the healthcare facility which people attend regularly, so they are subject to infection. The increase in infected patients leads to the increase in the risk that some patients won't finish their prescription rounds which in turn allows some of the bacteria to survive and develop a possible resistance. These surviving bacteria may repopulate, and may be ejected from the infected individuals via body fluids or excrement (Drugs in Drinking Water, (n.d.)). The bacteria may then end up in waste treatment facilities and agriculture in the form of reclaimed water where it is further exposed to antibiotics. This increase in exposure time of the bacteria to antibiotics leads to the higher chance developing resistant tendencies. These newly developed antibiotic resistant tendencies can then be shared with environmental bacteria and vice versa through the sharing of genetic material through plasmid exchange. This cycle receives positive feedback each time
antibiotic resistant bacteria reintroduced to the system, and the number of resistant strains of bacteria will continue to climb ever higher if they are not controlled.

However, not all of the factors are equal, and there is even some debate concerning which factors are more responsible than others. According to a recent study done by researchers at the University of Oxford, only 1 in 5 cases of Clostridium difficile, an antibiotic resistant bacteria, are contracted from in hospital settings from either the environment or fellow patients. The study shows that although important, hospital cases are not the number one cause of superbug cases, and that hospital infection control will not curb the infection. The study compared the genetic similarity between cases and determined that only 19% of all cases were linked to hospital or patient contact (Newswire, 2013). Conflicting data was presented in the New York Times which claimed that the majority of cases for MRSA were related to healthcare facilities (Sack, 2007). The World Health Organization claims the number one cause of antimicrobial resistance is the over use of bactericide, antimicrobials, and antibiotics. The factors may assume different levels of responsibility when it comes to different types of antibiotic resistant microbes. Some factors vary among individuals of a population. According to a study in the "Clinical Microbiology Reviews" some people may already carry non-resistant forms of a disease such as Staphylococcus aureus. The study found that those who carry the disease are more likely to contract methicillin-resistant Staphylococcus aureus infections. The study concluded that by eliminating the carried disease it reduces the chance for the resistant infection greatly (Lee, et al., 2012). A carried disease without symptoms would be subject to whatever antibiotics are give to the body whether the disease itself is the target which would encourage resistance. A large majority of the factors all have something in common, which was that the factors were affected either directly or indirectly by the widespread overuse of antibiotics and antimicrobial
substances. The best way to curb further resistance would be curb the apparent main factor involved which would be to end the widespread overuse of antibiotics.

Section 7: Controlling Antibiotic Resistant Superbugs

Of the many different factors at hand that lead to the emergence of antibiotic resistant bacteria, over usage would be most important factor to control. Many of these factors can be managed if over usage is stopped. In order for many of these solutions to achieve the desired effect in countries where there are large systems of institutionalized medicine, communication between involved parties is crucial and full cooperation is needed.

Political and Legal Restrictions

World governments can put antibiotic restrictions on agricultural industries to prevent the unnecessary overuse of antibiotics on livestock as preventative for infection. Antibiotics should only be introduced as a result of infection, not put in place without any obvious need. An instance is the Food and Drug Administration began drafting regulations on antibiotics used on animals in the food industry to help limit the growth or antibiotic resistant bacteria by limiting the widespread usage of antibiotics as of December 2013 (Strom, 2014). Also, governments could work together to monitor global outbreaks of antibiotic resistant strains to help contain the threat and to intervene so that the chance of further antibiotic resistance is diminished.

Regulation of Antimicrobials

Pharmacies and health organizations can remove over-the-counter antimicrobials and bactericides as well as monitor the number of prescribed antibiotics to ensure that they are only being prescribed for necessary cases and not for simple flu and cold cases which can be
FACTORS CONTRIBUTING TO ANTIBIOTIC RESISTANCE

recovered from in time (Get Smart: Know When Antibiotics Work, 2013). This regulation is important to contain the emergence of future strains of resistant bacteria and to help slow the growth of already antibiotic resistant pathogens. Additionally, health organization should agree upon what antibiotics are to be prescribed when, so there is plenty of antibiotic variation and bacteria are not able to adapt as quickly since their time of exposure to one specific antibiotic is limited.

Screening

Routine monitoring and screening of health facilities can ensure biofilms and superbugs are in check and not growing in clinical areas and surgical rooms and on surgical instruments. The monitoring would help keep hospital cases low. Also, screening could be done on patients to ensure that they are infection free after their antibiotic prescription regimen to prevent any lingering bacteria from building a resistance to the antibiotic.

Quarantine

Once infectious antibiotic resistant cases have been identified, they should be quarantined and isolated, not just to protect others in the healthcare facility, but to prevent the infected patient from interacting with other bacteria that may obtain the resistant gene through plasmid exchange (Conan, 2012). Quarantining outbreaks would help limit the global spread of superbugs, but it would not combat their sources.

Reminders/ Raising Awareness

One of the easiest factors to control is the "failure to complete prescription duration" factor. Reminders could be sent to patients to remind them to fully complete their prescription
regimen and to fully read and follow the directions indicated on the prescription bottle. Additionally, information campaigns could educate the public on this issue, so they are aware of the threat of simply forgetting to finish an antibiotic prescription or not fully completing the prescription duration. Finally, the storing and self-prescription of antibiotics should be strongly discouraged.

Health organizations could educate the public on the negative effects of antimicrobial hand soaps indicating they may contribute to the strength and resistance of superbugs. They should promote cleanliness and encourage hand washing with regular soaps which bond to bacteria and allows for it to be easily washed off (Perrone, 2013).

Elimination of Antimicrobials

Industries could find others ways to eliminate harmful microbes such as using ultraviolet light, intense heat, and other solutions that have a smaller risk of giving the bacteria an ability to build up resistance.

Also, cleaning and sanitation should be monitored to ensure sanitation is not taken to extreme levels and creating optimal environments for superbugs. Additionally harsh antimicrobials such as chemical-reliant hand sanitizer and antimicrobial soaps should be controlled, so it doesn't contribute to the super-sterile, competition-free, environment in which superbugs tend to thrive (Gucciardi, (n.d)).

Introduce more Antibiotics

Very few antibiotics have been developed and released since the 1980s which limits the supply of current antibiotics (Allott, A., 2014). The rising resistance could be curbed for a period
of time by introducing new antibiotics to combat the threat. This method of control will extend
the amount of time antibiotics will still be effective. The new antibiotics would need to either
target the mutated structure of the resistant bacteria or attack the bacteria in new ways that
bacteria isn’t resistant to yet. This method of control is practical but would seem to only prolong
the inevitable resistance if none of the other factors are monitored and controlled. A more stable
and long-term solution would be vaccines that encourage innate immunity (MacKenzie, 2006).

Section 8: Conclusion

Current habits with bactericides, antibiotics and their overall negligent usage are the
major factors for the increase in superbug emergence; everyday actions are responsible for the
presence of new and potentially life-threatening antibiotic resistant pathogens. Many antibiotic
resistant strains of bacteria originate in healthcare facilities where they were originally eradicated
due to constant exposure to antibiotics and antimicrobials. Since no antibiotics have been
introduced since the 1980s, the number of resistant strains is increasing due to lack of antibiotic
variation and the negligent use of the current antibiotics that we have today such (Allott, A.,
2014). Overexposure and overuse will allow bacteria to continue to exchange genetic resistance
to other species of bacteria if not contained and isolated from other environmental bacteria. In
order to deal with this emerging global health crisis, world governments must collaborate with
health organizations to educate the public and to put in place regulations and guidelines on
antibiotics and antimicrobials, so the emergence of new superbugs is slowed and future growth
of existing superbugs is hindered. This is a global issue that cannot be tackled by one party
alone; many of the solutions require active participation and intense supervision from a multitude
of different populations, governments, and organizations. There are many different factors, but if
antibiotic usage is closely monitored, then many of the resultant factors will be controlled.
Controlling over usage through a variety of public campaigns, regulations, and monitoring will have the largest and most immediate impact on the growth and spread of superbugs. Many of the proposed solutions that were outlined are practical in execution, but unfortunately, it is unlikely that all parties will cooperate to the extent needed to see a definite change until the matter worsens.
References


FACTORS CONTRIBUTING TO ANTIBIOTIC RESISTANCE


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