# Antimicrobial Resistance – The Global Threat: State of the Science

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## Abstract

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## Introduction

Before the discovery of antibiotics, millions of people died from a multitude of infectious diseases (IDs). Completely vulnerable populations died from tuberculosis (TB), syphilis, pneumonia, diphtheria and other IDs. Bacterial infections with *Staphylococcus* and *Streptococcus* had a sudden onset, progressed rapidly and were often fatal. In 1900, the 3 leading causes of death were pneumonia, TB and diarrhea/enteritis, with >30% of all deaths occurring in children <5 years old.[1] Prevalence of syphilis in the U.S. was estimated to be 5 to 10% in the general population, and as high as 25% in lower socioeconomic groups.[1] Medical science searched desperately for safe and effective antimicrobial drugs to treat these infections, which resulted in the trial of many formulations. Most of these had little or no efficacy, while some also caused serious, and sometimes fatal, adverse side effects. However, one formulation proved to be effective. In the early 1930s, sulfa drugs were found to have antibacterial properties and the sulfonamides became the first antibiotic drugs. Although these drugs were very limited in efficacy and caused numerous side effects, the sulfonamides started the antibiotic revolution in medicine. In 1928, Alexander Fleming observed that a culture of *Staphylococcus* aureus had been contaminated by a blue-green mold and bacterial colonies adjacent to the mold were killed. He isolated this mold, which he called penicillin, and found that it had significant antimicrobial properties.[1,2] By the early 1940s, penicillin proved to be much more effective and safer than sulfa drugs and was produced in substantial quantities for medical use.[1,2] The antibiotic era was born.

Penicillin quickly became the standard of care for most bacterial infections. During the 1950s and 1960s, new antibiotics were developed and immediately prescribed in clinical practice. During this "Golden Age of Antibiotics," death rates due to IDs in children <5 years of age plummeted from 30.4% in 1900 to 1.4% in 1997.[2] Between 1944 and 1954, rates of reported cases of syphilis decreased by more than 75%; by 1975, syphilis had declined by almost 90%.[2] Deaths from TB, diphtheria, Streptococcal and Staphylococcal infections, gonorrhea, and other IDs were dramatically reduced.[2] There was a 25% decline in deaths due to community-based pneumonia, a mortality decrease of 30% in hospital-based pneumonia, a 75% decrease in deaths from bacterial endocarditis (almost 100% fatal) and a 60% decrease in deaths from brain infection.[2] Additionally, mortality from complex skin infection was reduced by 3%. To put this into prospective, treatment of all heart attacks with aspirin and clot busting drugs combined has only reduced mortality by a total of 3%. Accompanied with other improvements in public health practices, such as immunizations and improvements in sanitation, housing and nutrition, antibiotics significantly contributed to the increased life expectancy of almost 30 years in the last century and radically reduced the morbidity and mortality from bacterial pathogens.[1]

The remarkable success of antibiotics cannot be overstated; however, their success, in large part, has contributed to their decreasing effectiveness. Almost immediately after introduction into clinical use, antimicrobial resistance (AMR) began to be reported.[3-6] However, the prevailing beliefs at the time were that:

1. Frequency of mutation to AMR would be too low to be of consequence
2. Resistance to more than 1 class of antibiotic at

the same time could not occur
3. Mutations to AMR would make bacteria less fit and virulent
4. Microorganisms were not capable of horizontal gene transfer[3-6]

All of these beliefs about AMR have been proven to be false and very little was done to address the issue of AMR. New antimicrobial drugs would be developed that would treat any emergent resistant infections and resistance to that drug would invariably develop. As the cornerstone of medicine, antibiotics were used almost universally to treat every type of infection in all disciplines of health care, regardless of the indication(s).[3-6] Today we are confronted with numerous, highly resistant organisms, some of which have developed novel resistance mechanisms that make it very difficult and more expensive to treat these infections.[3-6] Some organisms, commonly referred to as "superbugs," have developed such a high degree of resistance that antimicrobial agents remain ineffective.[3-6] Some infections from these superbugs, such as the carbapenem-resistant *Enterobacteriaceae,* are simply not treatable.[7]

An antimicrobial is a substance that kills or inhibits the growth of microorganisms (bacteria, virus, fungus, parasites).[3-6] AMR is defined as the ability of a microorganism to grow in the presence of a drug that would normally kill it or inhibit its growth, granting that particular bacteria, virus, fungus or other microbe the ability to resist the effects of an antibiotic/antimicrobial agent.[3-6] There are a multitude of mechanisms that lead to the development of AMR resulting in the partial or complete reduction of efficacy of the particular antimicrobial drug that was previously effective in killing the organism.[3-6] Once resistant organisms develop, they can rapidly replicate and pass to their progeny this newly acquired trait perpetuating the resistant strain.[3-6]

AMR is a worldwide problem and has resulted in a dramatic increase in antimicrobial-resistant health care-associated infections, as well as community-acquired infections.[3-6] The development of AMR is complex and multifactorial. However, 4 recognized and significant factors play a major role in the development of AMR:[3-6]

1. Indiscriminate/inappropriate use of antibiotic/antimicrobial agents in all health care settings
2. Overuse and/or misuse of antibiotics in farming/animal husbandry
3. Noncompliance with infection control practices
4. Adaptability of the organisms and natural biological changes (mutation and gene transfer)[3-6]

In order to survive in unfavorable environments, microorganisms are very adaptable and are constantly changing. Thus, the development of drug resistance is a natural evolutionary biological process.[3-6] When an organism is exposed to an antimicrobial agent, the organism is either killed or it is not. The surviving organisms are resistant and by natural selection, these organisms thrive.[3-6] Therefore, one of the most significant factors in the development of AMR has been the indiscriminate and inappropriate use of antibiotics which has occurred over many decades and in almost every health care setting.[3-6] Throughout the world, antibiotics, which act only on bacteria, are routinely and inappropriately prescribed for colds and other viral infections for which they are ineffectual and not indicated.[3,4] According to the World Health Organization, up to 50% of antimicrobial use is inappropriate.[4,6] Antibiotics are routinely:

1. Given when they are not needed
2. Continued when they are no longer necessary
3. Given at the wrong dose
4. Broad spectrum agents are used to treat very susceptible, non-resistant bacteria
5. The wrong antibiotic is given to treat an infection[4,6]

Additionally, the increase in the number of bootleg drugs has compounded the problem. Patients may be given drugs with little or no active drug, or even a different drug. In the U.S., the FDA estimates that 1% of prescription drugs are actually counterfeit. The Internet is a perfect avenue for the sale of bootleg or counterfeit pharmaceuticals.[6]

The excessive and widespread use of antibiotics in animals cannot be underestimated. Identical antibiotics/antimicrobials used in humans are also used extensively in all aspects of agriculture and veterinary medicine. Sub-therapeutic doses of antibiotics are used in animal industry to promote growth or prevent diseases.[6] This can result in resistant microorganisms which are transmissible to humans. It is estimated that as much as 70% of the antibiotics produced in the U.S. are used in animals.

Non-compliance with infection control amplifies and perpetuates drug resistance throughout a health care facility.[5,8,9] Health care workers' compliance with hand hygiene is low, usually around 40%. Needles are often reused, drugs are improperly administered, and reusable medical instruments and devices are not properly cleaned, disinfected and/or sterilized.[5,8,9] Clearly, improvement in compliance with standard precautions and safe injection practices is warranted and CDC recommendations

for infection control must be implemented and adhered to for every patient everyday.[5,8,9]

Finally, microorganisms can acquire AMR by development of a genetic mutation (biological evolution), some of which confer drug resistance to that organism.[3-6] Additionally, non-resistant bacteria receive the new DNA and become resistant to drugs by a process known as gene transfer, which can occur across multiple microbial species.[3-6]

In order to minimize the impact and development of drug resistance, all clinicians must prescribe antimicrobial drugs, inclusive of antibiotics, antifungals and antiviral agents, only when indicated and in the proper formulation and dosage.[5,8,9] Compliance with standard precautions and the principles of infection control as recommended by the CDC and other public health agencies must be enforced in every setting in which health care is performed.[5,8,9]

The purpose of this article is to raise clinician's awareness about the very grave problem that antimicrobial resistance poses in all health care settings (including dental) throughout the world. Translating the science and microbiology into clinical practice, while not addressed here, will require life-long learning, compliance to recommended guidelines and constant modification of how health care is delivered. The recent breach in fundamental infection control in a dental office in Oklahoma clearly illustrates the adverse sequellae of failure to comply with the principles of infection control and has prompted the following statement: "ADHA urges all dental hygienists to maintain the highest standards and employ the best practices for infection control."[10] The Organization for Safety, Asepsis and Prevention is a valuable asset that can help clinicians incorporate the state of the science into their dental practices.[11]

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