ANTIBIOTIC RESISTANCE

Prepared by:
Sonya Norris
Science and Technology Division
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INTRODUCTION

Human disease can result from the presence of harmful bacteria in the body. It is important to note that not all bacteria are harmful; in fact, most of the thousands of strains can be benign and in some cases even beneficial or

necessary to humans. Cases of disease-causing bacterial infection, however, are often treated with antibiotics.

Antibiotics are substances produced by micro-organisms (such as bacteria) that can harm or destroy other micro-organisms. The first antibiotic to be discovered, in in 1929 by Alexander Fleming, was penicillin. Its eventual production for commercial use in 1941 was a major medical development; for example, penicillin was instrumental in reducing deaths from infections during World War II. Antibiotics, which can now be produced synthetically, have been routinely prescribed for several decades for the treatment of diseases and ailments caused by bacterial infection. As a result of their exposure to antibiotics, a small proportion of harmful bacteria have developed resistance to them. This paper will review some of the circumstance surrounding this development.

WHAT IS ANTIBIOTIC RESISTANCE?

Antibiotic resistance is the ability of a bacterial strain to survive exposure to a specific antibiotic. It is not uncommon for a bacterial strain to become resistant to a number of antibiotic treatments but, generally, it will succumb eventually to one of the antibiotic drugs that we have available. Now that strains of bacteria are showing resistance to multiple drugs, however, many people fear that these and other strains will further evolve to develop resistance to the last remaining effective antibiotics. In fact, there are already three strains that are immune to the more than 100 antibiotic drugs. Once immune to the entire antibiotic arsenal, bacterial strains could produce devastating epidemics.

HOW HAS ANTIBIOTIC RESISTANCE COME ABOUT?

Antibiotics have historically been considered as "miracle drugs." Instead of being prescribed sparingly and taken properly, these drugs have been overwhelmingly used and misused. In some respects, the very nature of antibiotics promotes the development of resistance. Indeed, because of how these drugs work and the nature of bacteria, the problem of resistance now being observed should well have been predicted.

Bacteria can be described as being susceptible to, tolerant of, or resistant to specific antibiotics. When an antibiotic attacks a group of bacteria, those cells that are susceptible will die. Tolerant strains will cease to grow when exposed to the antibiotic; that is, they do not thrive but they are not killed. Normally, the effect of the drug on tolerant bacteria is sufficient to stop their growth and allow the body's own immune system to eliminate them. When the drug is discontinued too soon, however, the tolerant cells are allowed to proliferate and to repopulate the entire colony. Tolerance is often a precursor to resistance. Resistant strains of bacteria continue to thrive even when exposed to the drug. Thus, if antibiotic treatment ends and there are resistant cells left,

these will continue to thrive and cause another full blown infection, which this time will not be affected at all by the drug previously used. Additionally, antibiotics are self-defeating as they have the same effect on the non-harmful bacteria that are always present in the human body as they have on harmful bacteria. Non-pathogenic(1) bacteria that are antibiotic-resistant may then become a source for "resistance genes" by any newly invading harmful bacteria.

Bacteria can acquire tolerance and resistance in a number of different ways. Bacteria are very susceptible to genetic mutations and insertions from generation to generation. A strain of bacteria may for example pick up a resistance gene from viral DNA with which it is infected or by absorbing discarded genetic material containing a resistance gene from a bacterium that has died.

Many experts argue that antibiotic drugs have not been treated with the respect they deserve. Over-use, misuse and non-medical use of antibiotics are largely to blame for the problem of resistance since every exposure to antibiotics will encourage resistant strains of bacteria ¾ both pathogenic and non-pathogenic. Over-exposure, or over-use, must be minimized or eliminated. Many patients demand antibiotic prescriptions from doctors with no evidence that they are required and doctors sometimes acquiesce, in the belief that the drugs will do no harm. Additionally, it has been found that antibiotics are often prescribed before the presence of an infection has been verified. Another problem is that people tend to discontinue taking antibiotics as soon as they feel better, saving the unused portion for future self-medicating. Either way, improper dosing will fail to eliminate the disease agent completely and will encourage growth of both tolerant and resistant strains.

The recent proliferation of household products containing antibiotic agents will also promote the emergence of resistant strains. Moreover, almost half of all antibiotics produced are used in agriculture, being distributed in low doses in feed to promote livestock growth or sprayed as aerosols over crops (such as fruit trees) to prevent bacterial infestations. These uses also promote the growth of resistant strains, which can in turn enter a human body through unwashed hands or consumption of undercooked meat or unwashed fruits and vegetables.

WHAT ARE THE CONSEQUENCES OF ANTIBIOTIC RESISTANCE?

The potential consequences of the continued development of antibiotic-resistant bacteria could be severe. In fact, some experts have suggested that the situation, because of a larger human population, urbanization, widespread international travel, and the evolution of stronger strains of bacteria, could be worse than that before the discovery of penicillin. Diseases thought to have

been eradicated have re-emerged. Tuberculosis, for example, has proven to be more difficult to cure now than previously, due to the resistance acquired by the bacterium *Mycobacterium tuberculosis*. Without new methods for attacking them, potentially fatal bacterial infections could pose a serious threat to the world's population. Some of the most harmful diseases that can be caused by bacterial infection are pneumonia, meningitis, tuberculosis, endocarditis, sepsis, cholera, botulism and flesh-eating disease, while some of the frequent, non-lethal conditions for which antibiotics are prescribed are ear infections, urinary tract infections and strep throat.

CAN ANTIBIOTIC RESISTANCE BE OVERCOME?

There is some evidence to suggest that it may be possible to stop, or even reverse, the growing problem of antibiotic resistance; it can certainly be slowed down. One suggestion offered by experts in this area is that the non-medicinal use of antibiotics in agriculture should be discouraged or banned and new affordable alternatives found. Another suggestion is for physicians to ensure that antibiotics are prescribed only when it has been shown that they are required. Similarly, the proper use of these drugs must be emphasized, so that patients will finish their prescriptions. Other measures include making the public aware of the need to cook meat thoroughly, to wash raw fruits and vegetables carefully, and to reduce or eliminate use of household products said to be "antibacterial." Disease-causing germs can enter the body when unwashed hands touch the nose, mouth, or open wounds; thus, handwashing, both at home and in the clinical/hospital setting, is one of the easiest and most often overlooked methods of avoiding bacterial contamination.

It has been argued that bacterial resistance to antibiotics will persist until the public perception of bacteria is changed. Efforts to eliminate harmful infections must go along with deliberate efforts to permit the survival of non-pathogenic strains of bacteria, since killing the "good" bacteria gives the edge to the resistant strains.

WHAT IS BEING DONE TO OVERCOME ANTIBIOTIC RESISTANCE?

A. Canada

A superbug conference held in Montreal in 1997 produced an action plan for the establishment of a national body, now known as the Canadian Co-ordinating Committee on Antimicrobial Resistance (CCCAR). The Committee has recently received funding from the Laboratory Centre for Disease Control at Health Canada to establish a coordinated national strategy to monitor, control and reduce antibiotic resistance. CCCAR has identified three categories for action; 1) decreased use of antibiotics (both human and agricultural), 2) national surveillance of resistant strains, and 3) enhancement of regional, provincial and federal control programs. The Canadian External

Quality Assessment-Advisory Group on Antibiotic Resistance (CEQA-AGAR) within CCCAR primarily addresses testing for and reporting on antibacterial susceptibility to produce high quality data to support a national system for surveillance of antimicrobial resistance.

B. Elsewhere

The World Health Organisation (WHO) has an Antimicrobial Resistance Monitoring program which collaborates with the pharmaceutical industry to contain the spread of antibiotic-resistant bacteria. Denmark's surveillance has successfully reduced the proportion of antibiotic-resistant *Staphylococcus aureus* from 30% of hospital infections in the 1970s to 0.1% today. In Denmark, patients are routinely screened and immediately isolated if found to be infected. As well, older drugs are prescribed as the first line of bacterial treatment, leaving the newer drugs only as a last resort. All prescriptions for antibiotics are monitored. Other European countries with comprehensive antimicrobial resistance programs are Britain, France, Greece, Spain, Czech Republic, Italy and Sweden. The *Alliance for the Prudent Use of Antibiotics* is an international organization that monitors the emergence of antibiotic-resistant strains worldwide.

RESEARCH DEVELOPMENTS IN ANTIBIOTIC RESISTANCE

In response to the increased number of bacteria that have developed resistance to antibiotics, the pharmaceutical industry has greatly expanded its R&D in the search for alternatives. Some research findings suggested that antibiotics work by triggering a reaction in the bacteria leading to their own death and such a "suicide pathway" has now been confirmed. Bacteria that do not possess this technique are resistant to antibiotic treatment. Also, new drugs are being developed which interfere with the resistant cells' method of defence against certain antibiotics. For example, bacteria resistant to penicillin have been found to produce the enzyme penicillinase, which breaks up the penicillin before it can do its work. An inhibitor to this enzyme is now available. Given in tandem with penicillin, the inhibitor allows the penicillin to do its job, while at the same time preventing the penicillinase from destroying the antibiotic. Some of these new products are in clinical trials and should be available within two or three years while others are still at the development stage from which it is hoped they will progress to clinical trials in about five years.

CONCLUSION

The increased use, and sometimes misuse, of antibiotic drugs has resulted in bacterial resistance to a large and growing number of these drugs. Although research into newer antibiotics continues, measures can and should be taken to reverse the practices that promote development of antibiotic resistance in bacteria.

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(1) "Pathogenic" bacteria are disease-causing; "non-pathogenic" bacteria are normally occurring and harmless.