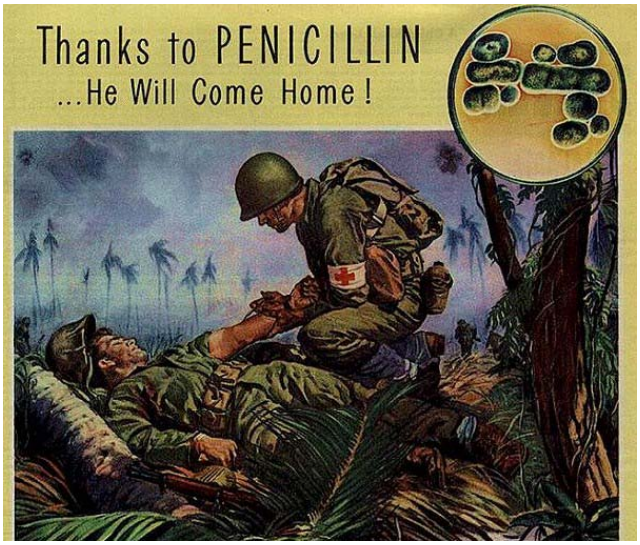

ANTIBIOTICS RESEARCH SUPPLEMENT

November 2, 2009

SIMPLE TRUTHS

WHITE PAPER RESEARCH LITERATURE SUPPLEMENT

PART I

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USANA Health Sciences

SUBJECT

Antibiotics – over-use, drug resistant organisms created from antibiotic use

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AVOIDING ANTIBIOTIC RESISTANCE EVOLUTION

MISSED ANTIBIOTIC DOSES LEAD TO INEFFECTIVE DRUGS

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May 27, 2008

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When antibiotic prescriptions are not followed, drug resistant bacteria evolve and antibiotics become less effective.

Did you know viruses not only plague humanity in the form of the common cold, influenza, and exotic diseases like Ebola- viruses also infect bacteria? In fact, those bacteria infecting you may also have a virus. Of course, Salmonella doesn't get a runny nose and E. coli isn't sneezing when infected by viruses known as bacteriophage.

Bacteriophage: Viruses Infecting Bacteria Contribute to Antibiotic Resistance

Bacteriophage takes their toll by a reduction in reproductive fitness. Infected bacteria do not multiply as rapidly and may have a more limited range of viability. Under most circumstances, uninfected bacteria dominate the population. But bacteriophage can confer special traits such as increased virulence and **antibiotic resistance**. In fact, the E. coli 0157:H7 that you fear in undercooked hamburger is so deadly precisely because it is infected with its own virus.

At times, these virus-infested bacteria gain the upper hand in bacterial reproduction. Many forms of antibiotic resistance are borne on a form of bacterial viruses called plasmids. When you take an antibiotic prescription to fight off bacterial infection, the uninfected bacteria are eliminated and bacterial strains with even the slightest resistance increase in number.

Proper Use of Antibiotics is Critical to Avoid Resistance

Two factors become critical when using antibiotics. You must take your doses on time and complete the whole course. If you miss a dose, your blood levels of antibiotic fall below the MIC, or minimum inhibitory concentration, and drug resistant bacteria will reproduce. When you

eventually take your next dose, the bacteria inhabiting your body will consist of a greater proportion of resistant strains and your medicine will be less effective.

What if you start feeling better and leave your antibiotic to gather dust in the medicine cabinet? Bacteria with greater antibiotic susceptibility are killed in the first few days of treatment, leaving those pesky resistant strains to be knocked out later in the course. There may be too few resistant bacteria present for you to feel sick, but with bacterial competition wiped out and lax adherence to your doctor's orders, in a few days they will multiply and you will feel sick again. This time your infection will consist predominantly of resistant strains and the next treatment may fail. That person you just coughed on also has the added bonus of infection with a drug resistant strain.

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THE "EVOLUTION" OF ANTIBIOTIC RESISTANCE

By Daniel Criswell, Ph.D*

Institute for Creation Research

http://www.icr.org/article/14/

* Dr. Daniel Criswell has a Ph.D. in Molecular Biology and is a biology professor at the ICR Graduate School.

An increase in the frequency of antibiotic resistance in bacteria since the 1950s has been observed for all major classes of antibiotics used to treat a wide variety of respiratory illnesses, skin disorders, and sexually transmitted diseases. Is this resistance the result of bacteria evolving new genes in response to the presence of antibiotics, or are antibiotic-resistant bacteria selected for in the environment by possessing antibiotic resistance genes beforehand? To answer these questions a discussion of several factors involved in antibiotic resistance will show that resistance is a designed feature of pre-existing genes enabling bacteria to compete with the antibiotic producers in their environment.

PENICILLIN AS AN EXAMPLE OF RESISTENCE

Tetracycline Resitance

Kanamycin Resistant Bacteria

A brief look at an example of penicillin resistance reveals the increase in the frequency of antibiotic-resistant organisms since the time when antibiotic use became common. Penicillin is an antibiotic produced by the common bread mold Penicillium that was discovered accidentally in 1929 by the British microbiologist, Alexander Fleming. By the 1940s, penicillin was available for medical use and was successfully used to treat infections in soldiers during World War II. Since then, penicillin has been commonly used to treat a wide range of infections. In

1967 the first penicillin-resistant Streptococcus pneumoniae was observed in Australia, and seven years later in the U.S. another case of penicillin-resistant S. pneumoniae was observed in a patient with pneumococcal meningitis.[1] In 1980 it was estimated that 3-5% of S. pneumoniae were penicillin-resistant and by 1998, 34% of the S. pneumoniae sampled were resistant to penicillin.1 Antibiotic resistance by other organisms reflects the same trend observed between S. pneumoniae and penicillin. Tetracycline resistance by normal human intestinal flora has exploded from 2% in the 1950s to 80% in the 1990s.[2] Kanamycin, an antibiotic used in the 1950s, has become clinically useless as a result of the prevalence of kanamycin-resistant bacteria. The increase in resistance among these organisms clearly indicates a change in the frequency of antibiotic resistance genes. Since World War II many more antibiotics isolated from fungi (molds) and bacteria have been used to treat a wide range of human and animal infections. One group of bacteria, the Streptomyces, produces most of the medically important antibiotics.[3] Streptomyces release antibiotics into the soil in a sort of "biochemical warfare" scenario to eliminate competing organisms from their environment. These antibiotics are small molecules that attack different parts of an organism's cellular machinery. Streptomyces-produced quinolone and coumarin antibiotics, such as novobiocin, interfere with a protein called gyrase that assists in the normal separation of double-stranded DNA during replication of DNA or transcription of messenger RNA.[4] Failure of DNA to properly separate during these processes results in a bacterium not being able to divide normally or produce functional proteins.

Ribosomes, the structures where protein synthesis is catalyzed, are the targets of many other Streptomyces antibiotics such as spectinomycin, tetracycline, and streptomycin. Spectinomycin and tetracycline prevent proteins from being assembled by the cell and streptomycin induces the assembly of the wrong amino acids into the translated protein.[5,6] Without proteins, which are necessary for normal cell function, the cell dies. The slight differences between human ribosomes which are not bound by these antibiotics and bacterial ribosomes make this type of antibiotic ideal for treating many illnesses. Other antibiotics, such as penicillin, block the assembly of the bacterial cell wall causing it to weaken and burst.[7] Penicillin is an effective antibiotic for human diseases because it interferes with a biological component in bacteria (cell wall) not found in human cells. The production of antibiotics by these organisms provides them with a competitive advantage over non-resistant bacteria in their environment. Just as large organisms such as plants and animals must compete for living space, food, and water, these microbes use antibiotics to eliminate competition with other microbes for these same resources.

However, not all bacteria are defenseless against the antibiotic producers. Many possess genes that encode proteins to neutralize the affects of antibiotics and prevent attacks on their cell machinery. Efflux pumps, located in the cell membrane, are one method of protection that many bacteria use against the influx of antibiotics.[6] The offensive antibiotic is pumped out of a cell that possesses these pumps before the antibiotic can cause harm to the cellular machinery. Although many efflux pumps may be specific for the substrate they pump out of the cell, they are not uncommon. Ribosomal protection proteins (RPP) are another source of resistance bacteria use to protect themselves from antibiotics. These proteins protect ribosomes by binding them and changing their shape

or conformation. The change in the ribosome shape prevents an antibiotic from binding and interfering with protein synthesis.6 The RPP-bound ribosomes are able to function normally during protein synthesis, an important feature of this method of antibiotic resistance. Some bacteria produce enzymes that neutralize antibiotics by adding acetyl (COCH3) or phosphate (PO32-) groups to a specific site on the antibiotic.[8] This modification reduces the ability of the antibiotic to bind to ribosomes, rendering it harmless to the cell.[9] Interestingly, all three types of antibiotic-resistant genes that produce efflux pumps, ribosomal protection proteins, and modifying enzymes are found in Streptomyces species, the producers of many antibiotics. It appears this is the method Streptomyces uses to protect itself from its own antibiotics.

Is it possible to transfer these resistance genes to other bacteria? A unique bacterial characteristic that has not been demonstrated in plant and animal cells is the ability to transfer genes from one bacterium to another, a process called lateral gene transfer. Genes located on a circular strand of DNA called an R-plasmid may contain several antibiotic-resistant genes. Through a process called conjugation an antibiotic-resistant bacterium can transfer the antibiotic resistance genes from an R-plasmid to a non-resistant bacterium.[10] Ironically, several antibiotic resistance genes found in other pathogenic bacteria are very similar in DNA sequence to the genes found in Streptomyces species.[11] The efflux pumps that Streptomyces use to pump out antibiotics to eliminate their competitors are likely the same pumps that other species of bacteria are now using to pump out the offensive antibiotic delivered from Streptomyces! The antibiotic-resistant bacteria likely have acquired the genes for these efflux pumps through lateral gene transfer. The presence of ribosomal protection proteins and antibiotic modifying enzymes in resistant bacteria has also likely originated from Streptomyces or some other antibiotic-producing microbe.6 Bacteria don't appear to be evolving new genes; they are acquiring previously existing antibiotic resistance genes through lateral gene transfer. This allows a species of bacteria to possess enough genetic variability to adapt to a changing environment and to compete with its neighbors. (This method of defense is very similar to the genetic variability of mammalian antibody-producing B lymphocytes—a topic for another Impact article.) The bacterium that acquires the antibiotic resistance genes still has the physical and metabolic qualities that distinguish it from other bacteria kinds and associates it with its own kind of bacteria. The observed increase in the frequency of antibiotic-resistant bacteria has resulted from the increased use of antibiotics in medicine and agriculture, resulting in the reduction of organisms that do not possess antibiotic resistance genes. Antibiotic resistance in bacteria can also be achieved when mutations in a ribosome or protein change the site where an antibiotic binds. For example, four of the antibiotics mentioned earlier, tetracycline, streptomycin, kanamycin, and spectinomycin, bind to a specific region of a ribosome and interfere with protein synthesis. Mutations may prevent an antibiotic from binding to the ribosome (kanamycin)[12] or allow the ribosome to function even while the antibiotic is bound (streptomycin and spectinomycin).[5] Although it appears these mutations are beneficial and provide an advantage to the bacterium possessing them, they all come with a cost. Ribosomal mutations, while providing antibiotic resistance for the organism, slow the process of protein synthesis, slow growth rates, and reduce the ability of the affected bacterium to compete in an environment devoid of a

specific antibiotic.[13,14] Furthermore, a mutation that confers resistance to one antibiotic may make the bacterium more susceptible to other antibiotics.[15] These deleterious effects are what would be expected from a creationist model for mutations. The mutation may confer a benefit in a particular environment, but the overall fitness of the population of one kind of bacterium is decreased as a result of a reduced function of one of the components in its biological pathway. The accumulation of mutations doesn't lead to a new kind of bacterium—it leads to extinction.

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EVOLUTION OF ANTIBIOTIC RESISTANCE

Evolution

PBS

http://www.pbs.org/wgbh/evolution/library/10/4/l_104_03.html

When a sick person takes antibiotics, the drugs begin to kill off the bacteria. But if treatment stops prematurely, it leaves some microbes alive -- the ones with mutations that make them resistant to the drugs. As these survivors multiply, they pass along their protective mutations to all their descendants. In this way, the bacteria evolves into a new drug-resistant strain.

Evolution of Antibiotic Resistance:

Forty or fifty years ago, thanks to antibiotics, scientists thought medicine had all but eradicated infectious agents as a major health threat. Instead, the past two decades have seen an alarming resurgence of infectious diseases and the appearance of new ones.

Today, the AIDS virus, tuberculosis, malaria, diarrheal diseases and other infectious agents pose far greater hazards to human existence than any other creatures.

This upsurge of infectious disease is a problem we have unwittingly created for ourselves. The rise of rapid, frequent, and relatively cheap international travel allows diseases to leap from continent to continent. Inadequate sanitation and lack of clean drinking water are another factor. A third is the "antibiotic paradox" -- the overuse of the "miracle drugs" to the point that they lose their potency.

Whenever antibiotics wage war on microorganisms, a few of the enemy are able to survive the drug. Because microbes are always mutating, some random mutation eventually will protect against the drug. Antibiotics used only when needed and as directed usually overwhelm the bugs. Too much antibiotic use selects for

more resistant mutants. When patients cut short the full course of drugs, the resistant strains have a chance to multiply and spread.

In some countries, such as the United States, patients expect and demand antibiotics from doctors, even in situations where they are inappropriate or ineffective. Our immune systems will cure many minor bacterial infections on their own, if given the chance, and antibiotics have no effect on viral infections at all. Every time antibiotics are used unnecessarily, they add to the selective pressure we are putting on microbes to evolve resistance. Then, when we really need antibiotics, they are less effective.

While drug companies race to develop new antibiotics that kill resistant microbes, scientists are urging patients and doctors to limit antibiotic use.

That means not asking for penicillin when all you have is a cold, since colds are caused by viruses that are not affected at all by antibiotics. It means taking all the pills that are prescribed, even if you're feeling better. Physicians have to resist prescribing the strongest and most broadly effective drugs unless the disease absolutely requires it. If society adopts these measures rigorously, the drugs may regain at least some of their lost "miracle" powers.

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ANTIBIOTIC RESISTANCE

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E! Science News
http://esciencenews.com/dictionary/antibiotic.resistant.bacterial.infections

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CALL TO ACTION: RUNNING OUT OF OPTIONS TO FIGHT EVER-CHANGING 'SUPER BUGS'
E! Science News
http://esciencenews.com/articles/2009/01/28/call.action.running.out.options.fight.ever.changing.super.bugs
Published: Wednesday, January 28, 2009 - 17:58 in Health & Medicine
Source: University of Texas Health Science Center at Houston

People are dying from "super bugs" because our antibiotic arsenal has run dry, leaving the world without sufficient weapons to fight ever-changing bacteria, warn infectious disease researchers at The University of Texas Medical School at Houston. In a Jan. 29 perspective in *The New England Journal of Medicine*, Barbara E.

Murray, M.D., and Cesar Arias, M.D., Ph.D., evaluate the past, present and future response to preventing and treating "super bugs."

A "super bug" is an organism that is resistant to antibiotics. It can evade antibiotics by:

- destroying the medication by producing an enzyme that devours the drug;
- creating a barrier to the drug;
- pumping out any antibiotic that reaches the bacterial cell;
- modifying the target of the antibiotic so the drug can't bind to it.

"Most of the public has heard of MRSA (methicillin-resistant*Staphylococcus aureus*) because it produces the most cases each year. However, they have not heard of other super bugs that can be far worse," said Murray, co-author and director of Division of Infectious Diseases at the UT Medical School. "The Gram-negative bacteria are the most antibiotic-resistant with fewer treatment options in life-threatening diseases, such as certain forms of pneumonia, bloodstream infections, gastroenteritis and even meningitis." Gram-negative bacteria can release toxins created by their cell walls into the bloodstream, where it is harder to treat them.

According to a 2004 report, "Bad Bugs, No Drugs," by the Infectious Diseases Society of America (IDSA), none of the 89 new drugs approved by the U.S. Food and Drug Administration were antibiotics. Murray and Arias say people are also taking antibiotics without prescriptions or not following the prescription as directed. It is those practices that allow the antibiotics to be exposed to a wide-range of bacteria in the body, both good and bad, which gives the bugs an opportunity to find ways to beat antibiotic weapons.

"We have run out of options. The promise of genomics (Note: *the study of genomes*) has not panned out. Gene sequencing has not helped us find a better way to fight these bugs," said Murray, holder of the J. Ralph Meadows Professorship in Internal Medicine at the medical school. Genomics is the study of an organism's genomes to chart its DNA sequencing.

According to the IDSA's 2004 report, the research on new antibiotics is simply drying up, in part due to the expense of bringing a new drug to market. "The pharmaceutical companies, like all other publicly traded industries, must deliver to its shareholders in order to justify their continued investment. The unique nature of antibiotics makes securing investments challenging. Because antibiotics work so well and so fast, they produce a weak return on investment for manufacturers. Antibiotics are commonly prescribed for seven to 14 days," the report said.

"Academics can't do it all. Pharmaceutical companies can't do it all. Everyone needs to work together to address this potential worldwide public health crisis," said Arias, co-author of the perspective and assistant professor in infectious diseases at the medical school.

Delay in diagnosis is also an issue. Murray said even with advancements, it takes about 48 hours or more from the time a culture is taken to determine what a person may have contracted and to determine what antibiotics are likely to be effective. "It may not sound like a lot of time, but with some of these bugs you have to move quickly to save a patient. You don't want the bacteria to spread. Research needs to include finding new testing methods," Murray said.

The Division of Infectious Diseases at the UT Medical School is already working toward solutions. It has now established the Laboratory for Antimicrobial Research, headed by Arias, within the Center for the Study of Emerging and Re-Emerging Pathogens, headed by Murray. The laboratory, which is supported with funding from the National Institutes of Health (NIH), aims to investigate the clinical and molecular aspects of antibiotic resistance, attempting to understand the complex mechanisms by which bugs become resistant to antibiotics and then designing new strategies to combat them.

"We are struggling, really struggling to treat patients around the world. If something isn't done soon, more and more bugs are going to gain the upper-hand. There are simply not enough new drugs to keep pace with antibiotic-resistant bacterial infections," Murray said. "We are sounding the alarm, and hopefully the world will hear it."

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THE RISE OF ANITBIOTIC-RESISTANT INFECTIONS

*by Ricki Lewis, Ph.D**

http://dwb4.unl.edu/Chem/CHEM869K/CHEM869KLinks/www.fda.gov/fdac/features/795_antibio.html

**Ricki Lewis is a geneticist and textbook author.*

When penicillin became widely available during the second world war, it was a medical miracle, rapidly vanquishing the biggest wartime killer--infected wounds. Discovered initially by a French medical student, Ernest Duchesne, in 1896, and then rediscovered by Scottish physician Alexander Fleming in 1928, the product of the soil mold Penicillium crippled many types of disease-causing bacteria. But just four years after drug companies began mass-producing penicillin in 1943, microbes began appearing that could resist it.

The first bug to battle penicillin was Staphylococcus aureus. This bacterium is often a harmless passenger in the human body, but it can cause illness, such as pneumonia or toxic shock syndrome, when it overgrows or produces a toxin.

In 1967, another type of penicillin-resistant pneumonia, caused by Streptococcus pneumoniae and called pneumococcus, surfaced in a remote village in Papua New Guinea. At about the same time, American military personnel in southeast Asia were acquiring penicillin-resistant gonorrhea from prostitutes. By 1976, when the soldiers had come home, they brought the new strain of gonorrhea with them, and physicians had to find new drugs to treat it. In 1983, a hospital-acquired intestinal infection caused by the bacterium Enterococcus faecium joined the list of bugs that outwit penicillin.

Antibiotic resistance spreads fast. Between 1979 and 1987, for example, only 0.02 percent of pneumococcus strains infecting a large number of patients surveyed by the national Centers for Disease Control and Prevention were penicillin-resistant. CDC's survey included 13 hospitals in 12 states. Today, 6.6 percent of pneumococcus strains are resistant, according to a report in the June 15, 1994, Journal of the American Medical Association by Robert F. Breiman, M.D., and colleagues at CDC. The agency also reports that in 1992, 13,300 hospital patients died of bacterial infections that were resistant to antibiotic treatment.

Why has this happened?

"There was complacency in the 1980s. The perception was that we had licked the bacterial infection problem. Drug companies weren't working on new agents. They were concentrating on other areas, such as viral infections," says Michael Blum, M.D., medical officer in the Food and Drug Administration's division of anti-infective drug products. "In the meantime, resistance increased to a number of commonly used antibiotics, possibly related to overuse of antibiotics. In the 1990s, we've come to a point for certain infections that we don't have agents available."

According to a report in the April 28, 1994, New England Journal of Medicine, researchers have identified bacteria in patient samples that resist all currently available antibiotic drugs.

Survival of the Fittest

The increased prevalence of antibiotic resistance is an outcome of evolution. Any population of organisms, bacteria included, naturally includes variants with unusual traits--in this case, the ability to withstand an antibiotic's attack on a microbe. When a person takes an antibiotic, the drug kills the defenseless bacteria, leaving behind--or "selecting," in biological terms--those that can resist it. These renegade bacteria then multiply, increasing their numbers a million-fold in a day, becoming the predominant microorganism.

The antibiotic does not technically cause the resistance, but allows it to happen by creating a situation where an already existing variant can flourish. "Whenever antibiotics are used, there is selective pressure for resistance to occur. It builds upon itself. More and more organisms develop resistance to more and more drugs," says Joe

Cranston, Ph.D., director of the department of drug policy and standards at the American Medical Association in Chicago.

A patient can develop a drug-resistant infection either by contracting a resistant bug to begin with, or by having a resistant microbe emerge in the body once antibiotic treatment begins. Drug-resistant infections increase risk of death, and are often associated with prolonged hospital stays, and sometimes complications. These might necessitate removing part of a ravaged lung, or replacing a damaged heart valve.

Bacterial Weaponry

Disease-causing microbes thwart antibiotics by interfering with their mechanism of action. For example, penicillin kills bacteria by attaching to their cell walls, then destroying a key part of the wall. The wall falls apart, and the bacterium dies. Resistant microbes, however, either alter their cell walls so penicillin can't bind or produce enzymes that dismantle the antibiotic.

In another scenario, erythromycin attacks ribosomes, structures within a cell that enable it to make proteins. Resistant bacteria have slightly altered ribosomes to which the drug cannot bind. The ribosomal route is also how bacteria become resistant to the antibiotics tetracycline, streptomycin and gentamicin.

How Antibiotic Resistance Happens

Antibiotic resistance results from gene action. Bacteria acquire genes conferring resistance in any of three ways. In spontaneous DNA mutation, bacterial DNA (genetic material) may mutate (change) spontaneously (indicated by starburst). Drug-resistant tuberculosis arises this way.

In a form of microbial sex called transformation, one bacterium may take up DNA from another bacterium. Pencillin-resistant gonorrhea results from transformation. Most frightening, however, is resistance acquired from a small circle of DNA called a plasmid, that can flit from one type of bacterium to another. A single plasmid can provide a slew of different resistances. In 1968, 12,500 people in Guatemala died in an epidemic of Shigella diarrhea. The microbe harbored a plasmid carrying resistances to four antibiotics!

A Vicious Cycle: More Infections and Antibiotic Overuse

Though bacterial antibiotic resistance is a natural phenomenon, societal factors also contribute to the problem. These factors include increased infection transmission, coupled with inappropriate antibiotic use.

More people are contracting infections. Sinusitis among adults is on the rise, as are ear infections in children. A report by CDC's Linda F. McCaig and James M. Hughes, M.D., in the Jan. 18, 1995, Journal of the American Medical Association, tracks antibiotic use in treating common illnesses. The report cites nearly 6 million antibiotic

prescriptions for sinusitis in 1985, and nearly 13 million in 1992. Similarly, for middle ear infections, the numbers are 15 million prescriptions in 1985, and 23.6 million in 1992.

Causes for the increase in reported infections are diverse. Some studies correlate the doubling in doctor's office visits for ear infections for preschoolers between 1975 and 1990 to increased use of day-care facilities. Homelessness contributes to the spread of infection. Ironically, advances in modern medicine have made more people predisposed to infection. People on chemotherapy and transplant recipients taking drugs to suppress their immune function are at greater risk of infection.

"There are the number of **immuno-compromised** patients, who wouldn't have survived in earlier times," says Cranston. "Radical procedures produce patients who are in difficult shape in the hospital, and are prone to nosocomial [hospital-acquired] infections. Also, the general aging of patients who live longer, get sicker, and die slower contributes to the problem," he adds..

Though some people clearly need to be treated with antibiotics, many experts are concerned about the inappropriate use of these powerful drugs. "Many consumers have an expectation that when they're ill, antibiotics are the answer. They put pressure on the physician to prescribe them. Most of the time the illness is viral, and antibiotics are not the answer. This large burden of antibiotics is certainly selecting resistant bacteria," says Blum. Another much-publicized concern is use of **antibiotics in livestock,** where the drugs are used in well animals to prevent disease, and the animals are later slaughtered for food. "If an animal gets a bacterial infection, growth is slowed and it doesn't put on weight as fast," says Joe Madden, Ph.D., strategic manager of microbiology at FDA's Center for Food Safety and Applied Nutrition. In addition, antibiotics are sometimes administered at low levels in feed for long durations to increase the rate of weight gain and improve the efficiency of converting animal feed to units of animal production.

FDA's Center for Veterinary Medicine limits the amount of antibiotic residue in poultry and other meats, and the U.S. Department of Agriculture monitors meats for drug residues. According to Margaret Miller, Ph.D., deputy division director at the Center for Veterinary Medicine, the residue limits for antimicrobial animal drugs are set low enough to ensure that the residues themselves do not select resistant bacteria in (human) gut flora.

FDA is investigating whether bacteria resistant to quinolone antibiotics can emerge in food animals and cause disease in humans. Although thorough cooking sharply reduces the likelihood of antibiotic-resistant bacteria surviving in a meat meal to infect a human, it could happen. Pathogens resistant to drugs other than fluoroquinolones have sporadically been reported to survive in a meat meal to infect a human. In 1983, for example, 18 people in four midwestern states developed multi-drug-resistant Salmonella food poisoning after eating beef from cows fed antibiotics. Eleven of the people were hospitalized, and one died.

A study conducted by Alain Cometta, M.D., and his colleagues at the Centre Hospitalier Universitaire Vaudois in Lausanne, Switzerland, and reported in the April 28, 1994, New England Journal of Medicine, showed that increase in antibiotic resistance parallels increase in antibiotic use in humans. They examined a large group of cancer patients given antibiotics called fluoroquinolones to prevent infection. The patients' white blood cell counts were very low as a result of their cancer treatment, leaving them open to infection.

Between 1983 and 1993, the percentage of such patients receiving antibiotics rose from 1.4 to 45. During those years, the researchers isolated Escherichia coli bacteria annually from the patients, and tested the microbes for resistance to five types of fluoroquinolones. Between 1983 and 1990, all 92 E. coli strains tested were easily killed by the antibiotics. But from 1991 to 1993, 11 of 40 tested strains (28 percent) were resistant to all five drugs.

Towards Solving the Problem

Antibiotic resistance is inevitable, say scientists, but there are measures we can take to slow it. Efforts are under way on several fronts--improving infection control, developing new antibiotics, and using drugs more appropriately.

Barbara E. Murray, M.D., of the University of Texas Medical School at Houston writes in the April 28, 1994, New England Journal of Medicine that simple improvements in public health measures can go a long way towards preventing infection. Such approaches include more frequent hand washing by health-care workers, quick identification and isolation of patients with drug-resistant infections, and improving sewage systems and water purity in developing nations.

Drug manufacturers are once again becoming interested in developing new antibiotics. These efforts have been spurred both by the appearance of new bacterial illnesses, such as Lyme disease and Legionnaire's disease, and resurgences of old foes, such as tuberculosis, due to drug resistance.

FDA is doing all it can to speed development and availability of new antibiotic drugs. "We can't identify new agents--that's the job of the pharmaceutical industry. But once they have identified a promising new drug for resistant infections, what we can do is to meet with the company very early and help design the development plan and clinical trials," says Blum.

In addition, drugs in development can be used for patients with multi-drug-resistant infections on an "emergency IND (compassionate use)" basis, if the physician requests this of FDA, Blum adds. This is done for people with AIDS or cancer, for example.

No one really has a good idea of the extent of antibiotic resistance, because it hasn't been monitored in a coordinated fashion. "Each hospital monitors its own resistance, but there is no good national system to test for antibiotic resistance," says Blum.

This may soon change. CDC is encouraging local health officials to track resistance data, and the World Health Organization has initiated a global computer database for physicians to report outbreaks of drug-resistant bacterial infections.

Experts agree that antibiotics should be restricted to patients who can truly benefit from them--that is, people with bacterial infections. Already this is being done in the hospital setting, where the routine use of antibiotics to prevent infection in certain surgical patients is being reexamined.

"We have known since way back in the antibiotic era that these drugs have been used inappropriately in surgical prophylaxis [preventing infections in surgical patients]. But there is more success [in limiting antibiotic use] in hospital settings, where guidelines are established, than in the more typical outpatient settings," says Cranston. Murray points out an example of antibiotic prophylaxis in the outpatient setting--children with recurrent ear infections given extended antibiotic prescriptions to prevent future infections. (See "Protecting Little Pitchers' Ears" in the December 1994 FDA Consumer.)

Another problem with antibiotic use is that patients often stop taking the drug too soon, because symptoms improve. However, this merely encourages resistant microbes to proliferate. The infection returns a few weeks later, and this time a different drug must be used to treat it.

Targeting TB

Stephen Weis and colleagues at the University of North Texas Health Science Center in Fort Worth reported in the April 28, 1994, New England Journal of Medicine on research they conducted in Tarrant County, Texas, that vividly illustrates how helping patients to take the full course of their medication can actually lower resistance rates. The subject--tuberculosis.

TB is an infection that has experienced spectacular ups and downs. Drugs were developed to treat it, complacency set in that it was beaten, and the disease resurged because patients stopped their medication too soon and infected others. Today, one in seven new TB cases is resistant to the two drugs most commonly used to treat it (isoniazid and rifampin), and 5 percent of these patients die.

In the Texas study, 407 patients from 1980 to 1986 were allowed to take their medication on their own. From 1986 until the end of 1992, 581 patients were closely followed, with nurses observing them take their pills. By the

end of the study, the relapse rate--which reflects antibiotic resistance--fell from 20.9 to 5.5 percent. This trend is especially significant, the researchers note, because it occurred as risk factors for spreading TB--including AIDS, intravenous drug use, and homelessness--were increasing. The conclusion: Resistance can be slowed if patients take medications correctly.

Narrowing the Spectrum

Appropriate prescribing also means that physicians use "narrow spectrum" antibiotics--those that target only a few bacterial types--whenever possible, so that resistances can be restricted. The only national survey of antibiotic prescribing practices of office physicians, conducted by the National Center for Health Statistics, finds that the number of prescriptions has not risen appreciably from 1980 to 1992, but there has been a shift to using costlier, broader spectrum agents. This prescribing trend heightens the resistance problem, write McCaig and Hughes, because more diverse bacteria are being exposed to antibiotics.

One way FDA can help physicians choose narrower spectrum antibiotics is to ensure that labeling keeps up with evolving bacterial resistances. Blum hopes that the surveillance information on emerging antibiotic resistances from CDC will enable FDA to require that product labels be updated with the most current surveillance information.

Many of us have come to take antibiotics for granted. A child develops strep throat or an ear infection, and soon a bottle of "pink medicine" makes everything better. An adult suffers a sinus headache, and antibiotic pills quickly control it. But infections can and do still kill. Because of a complex combination of factors, serious infections may be on the rise. While awaiting the next "wonder drug," we must appreciate, and use correctly, the ones that we already have.

The Greatest Fear--Vancomycin Resistance

When microbes began resisting penicillin, medical researchers fought back with chemical cousins, such as methicillin and oxacillin. By 1953, the antibiotic armamentarium included chloramphenicol, neomycin, terramycin, tetracycline, and cephalosporins. But today, researchers fear that we may be nearing an end to the seemingly endless flow of antimicrobial drugs.

At the center of current concern is the antibiotic vancomycin, which for many infections is literally the drug of "last resort," says Michael Blum, M.D., medical officer in FDA's division of anti-infective drug products. Some hospital-acquired staph infections are resistant to all antibiotics except vancomycin.

Now vancomycin resistance has turned up in another common hospital bug, enterococcus. And since bacteria swap resistance genes like teenagers swap T-shirts, it is only a matter of time, many microbiologists believe, until

vancomycin-resistant staph infections appear. "Staph aureus may pick up vancomycin resistance from enterococci, which are found in the normal human gut," says Madden. And the speed with which vancomycin resistance has spread through enterococci has prompted researchers to use the word "crisis" when discussing the possibility of vancomycin-resistant staph.

Vancomycin-resistant enterococci were first reported in England and France in 1987, and appeared in one New York City hospital in 1989. By 1991, 38 hospitals in the United States reported the bug. By 1993, 14 percent of patients with enterococcus in intensive-care units in some hospitals had vancomycin-resistant strains, a 20-fold increase from 1987. A frightening report came in 1992, when a British researcher observed a transfer of a vancomycin-resistant gene from enterococcus to Staph aureus in the laboratory. Alarmed, the researcher immediately destroyed the bacteria.

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WHAT DOESN'T KILL THEM MAKES THEM STRONGER - WHEN ANTIBIOTICS QUIT WORKING
NISE
http://whyfiles.org/038badbugs/

Overuse antibiotics and bacteria can become resistant to them. But could use of household disinfectants cause the same problem? That's what a New Jersey high school student suspects. [Posted May 1, 1997]

Bacterial boomerang
Do common household disinfectants spark antibiotic resistance in bacteria? That's the question Merri Moken, of Morristown, N. J., began asking four years ago. Merri, 17, was too busy to talk to The Why Files, but her mother, Carol, explained that she'd exposed bacteria to disinfectants like hydrogen peroxide and chlorine bleach.
The bacteria, faced with a deadly assault (would you want to slurp bleach?), nevertheless figured out a survival strategy. "She was seeing selective mutations that were 100 percent resistant," says Carol Moken. Merri then used electrophoresis (defined) to see what parts of the bacteria were changed during that mutation process. Finally, she identified the genes she thinks are responsible for the resistance.

This year, Merri was named a finalist in the 56th Westinghouse Science Talent Search -- the Nobel of science prizes for young people -- for her efforts.

The possibility that common disinfectants could spark resistance in bacteria could have broad ramifications in an era of increased usage of disinfectants. Bug-resistant steering wheels, bug-resistant toys, bug-resistant toothbrushes -- it's as if we'd lost our innate ability to fight disease. Are we going bats over bugs?

Carol says Merri's work is being taken seriously by the Food and Drug Administration, researchers at Tufts University, and now The Why Files.

Are you saying antibiotic resistance is a real problem?

How big a problem?

What happened to antibiotics? Once considered the universal answer to infectious disease, we now know the effective life span of these once-miraculous drugs is limited. The problem, simply, is that we "got complacent," says Barry Kreiswirth of the Public Health Research Institute, who makes a living analyzing strains of tuberculosis that resist as many as nine antibiotics.

It's not just TB. "The global increase in resistance to antimicrobial drugs, including the emergence of bacterial strains that are resistant to all available antibacterial agents, has created a public health problem of potentially crisis proportions." That's the word from the American Medical Association (AMA), which studied the issue in 1995, and seldom fulminates (defined) in such alarmist terms.

The very success of antibiotics accounts for part of the resistance problem, argues Julian Davies of the University of British Columbia. The life-saving drugs have "changed the way diseases have been treated." It's not only that they are sometimes used to treat viral infections, against which they are impotent. It's also that they are used as "props" when safer methods [think of sanitation or quarantine (defined) might be preferable.

The experts are sounding the alarm about antibiotic resistance because of grim new evidence:
Resistance happens **quickly**, in parallel with the use of antibiotics. An 11-year study of cancer patients at a hospital in Switzerland (see the 4/28/94 New England Journal of Medicine) found that no strains of Escherichia coli (a common intestinal bacteria that can be pathogenic) resisted any of the fluoroquinolone antibiotics between 1983 and 1990. But between 1991 and 1993, 28 percent of the strains tested were resistant to **all five** of them. During the study period, the percentage of patients getting antibiotics rose from 1.4 percent to 45 percent. (**Updated 1 May, 1998**: Under a new National Institutes of Health grant, scientists have begun examining whether harmless bacteria carry resistance genes and transmit them to pathogens. Already, it's thought that the bacterium Haemophilus influenzae, which causes ear infections, gained resistance to the antibiotic ampicillin during a gene transfer from Escherichia coli, during the 1970s. Why would a harmless bacterium acquire such resistance? Because any organism exposed to antibiotics faces the same selective pressure that causes pathogens to become antibiotic resistant. One leader of the new research group, University of Illinois at Urbana-Champaign microbiologist Abigail Salyers, said resistance can lurk undetected in harmless organisms. She called the presence of resistance in pathogens "the tip of the iceberg compared to what's out there in the environment." See "New Hunt for the Roots of Resistance," Science, 3 April 1998, p. 27. **End update**.)

It's **widespread**. In Atlanta, a 1994 study of infections caused by Streptococcus pneumonia found that 25 percent of 431 patients had a bug that resisted penicillin, and that 25 percent of all cases were resistant to several antibiotics.

It **spreads fast**: thanks in part to jet planes. Resistant tuberculosis has spread from New York City to Denver, Florida, Nevada and Paris.

Bacteria **learn from our mistakes**: Once resistance develops, all offspring of that bacterium get it. "Once the resistant strain is made, everybody who is infected with it will have that resistance problem," says Kreiswirth. And because these organisms then pick up further resistance to other drugs, he says, "All it's going to do is get worse." You can skip ahead to our coverage of the mechanisms of resistance.

Hospitals serve as centers for the formation and transmission of drug-resistant organisms. About 2 million Americans are infected in hospitals each year and more than half of these infections resist at least one antibiotic, according to Dennis Maki, a University of Wisconsin-Madison expert in hospital infections. In 1992, 13,300 hospital patients were killed by drug-resistant bacteria in the United States.

Resistance is an especially vexing problem for people with **impaired immune systems**, such as AIDS, and cancer patients, and recipients of organ transplants. About 90 percent of AIDS patients who get multiple-drug resistant TB die.

Even the last-ditch antibiotics are being overwhelmed. Of particular concern is Vancomycin resistance, which is becoming fairly common in certain strains of enterococcus, a common gut bacteria. While enteroccocci generally do not cause life-threatening disease, the gene for the resistance may spread to more deadly organisms like Staphylococcus aureus. That transfer has already taken place in a lab dish and could occur elsewhere.
Multiple resistance, multiple causes

Any time bacteria are exposed to an antibiotic, they are under "selective pressure" that allows only resistant forms to survive and reproduce. So the basic rule in slowing the evolution of resistance is reducing the unnecessary use of antibiotics.

A key problem is the routine feeding of antibiotics to **farm animals:** Davies notes that, by weight, half of all antibiotics are given to livestock and fish in a prophylactic attempt to prevent disease. That argument gets support from a new report by the CDC Morbidity and Mortality Weekly Report, on Multidrug-Resistant Salmonella, serotype Typhimurium. Let's quote from this alarming document:

"A drug-resistant Salmonella Typhimurium subtype, associated with severe human illness, has emerged in the United States... A new emerging subtype, known as S. Typhimurium Definitive Type 104 (DT 104), characterized by multiple antimicrobial resistance, has been present in the United Kingdom since 1984... Studies in the United Kingdom showed that S. Typhimurium is present in animals (farm, wild, and pets), and that it can be transmitted from farm animals and pets to humans. Those studies also showed that eating beef, pork, or poultry products have been associated with outbreaks of disease in people... S. Typhimurium DT 104 has been detected recently in the United States, and its incidence and distribution are being actively studied to assess and address the threat to public health."

OVER THE COUNTER ANTIBIOTICS

In at least half the world, **antibiotics can be sold over-the-counter**, Davies adds. That's something many experts suggest should be avoided.

Overuse at your peril

Yet even in places where antibiotics require a physician's prescription, there's a tendency to overuse them, Davies says. One danger zone, he says, is the prophylactic (defined) use of antibiotics during surgery. "Surgeons are not infectious disease people, and while they may rightly feel that their patients are at risk if they don't use antibiotics prophylactically, whether that's really good, I don't know." Again, such widespread use is likely to foster the evolution of resistant strains.

Instead of relying on antibiotics, Davies suggests that **surgeons "ought to be able to set up an operating theater so it is sterile,** so there is no opportunity for infection. That should not be out of the question."
Surgeons have been changing their practice over the past few years, according to Joe Cranston of the American Medical Association. "Clearly there was a move toward shorter time frame for prophlyaxis" in surgery, with as little as one dose being given just before surgery begins.

So what do we know about how bacteria perform these nasty transformations?

It's all in the teamwork

How do microbes "learn" to defeat antibiotics? That's a feverishly important question in an era of mounting resistance to life-saving drugs. Unfortunately, the answers are disturbing.
"Molecular biology is telling us ... what the resistance mechanisms are, although we don't know all the details," says microbiologist Julian Davies of the University of British Columbia. Most people probably figure that bacteria rely on mutations to gain resistance to antibiotics.
Here's new information on the number of bacteria on Earth.

Mutations do come into play when drug manufacturers modify an existing antibiotic to overcome resistant bugs. In that case, the bacteria already possess a gene to defeat the antibiotic, and it mutates to regain mastery over the modified antibiotic.

Bacteria acquire genes for resistance in three ways.

1. In spontaneous mutation, bacterial DNA may change spontaneously, as indicated by the starburst. Drug-resistant tuberculosis arises this way.

2. In a form of microbial sex called transformation, one bacterium may take up DNA from another. Penicillin-resistant gonorrhea (defined) results from transformation.

3. Most frightening, however, is resistance acquired from a small circle of DNA called a plasmid. Plasmids can flit between bacteria of various types -- they generally must be touching -- and carry multiple resistance. In 1968, 12,500 Guatemalans died in an epidemic of Shigella diarrhea, caused by a microbe harboring a plasmid that conferred resistances to four antibiotics!

But bacteria do something much more clever than just mutating. That's chancy, so bacteria prefer to share biochemical secrets -- resistance genes -- that enable them to resist or destroy antibiotics.
This diabolical bartering can occur in a couple of ways.

1. Some bacteria share **plasmids** -- small chunks of DNA, like mini-chromosomes -- that exist outside the main chromosomes. This sharing can leap broad divisions in bacterial phylogeny (defined). It's almost as if a cow could lend a crow a gene and teach it to grow teeth.

2. Gene cassettes are genes that can be spliced in the chromosomes (defined). While the mechanism is kind of complex, it can be compared to an expedition to a shopping mall, Davies says. Genes called integrons code for enzymes called integrases that can splice those cassettes into chromosomes or other genetic material where they become functional. That makes the integrons function something like a shopping cart, Davies says.
If bacteria can obtain resistance merely by accepting gene cassettes, then, like shoppers in a video store who aren't sure if they've seen their first selection, bacteria can pick up several cassettes and obtain resistance to several antibiotics.

>> Furthermore, says microbiologist Abigail Salyers of the University of Illinois, **"**Bacteria also integrate resistance to disinfectants or to pollutants in these clusters. Thus disinfectant use or pollution can select for antibiotic resistance, which could be exactly what Merri Moken was finding back at the start of our story.

From the human point of view, the problem with this kind of resistance is its permanence. Once lodged inside the chromosome or plasmid, these resistance genes are distributed as normal genes to all daughter (defined) cells. "Origin and Interstate Spread..." in the bibliography gives a detailed picture of how a deadly bug that causes tuberculosis gained resistance to many antibiotics.

Mechanisms

So far, we've talked generally about resistance without painting a good picture of how it works. And here we're in for yet another surprise, yet more evidence of what might be called the microbial mind. It turns out that antibiotic resistance is part of a larger picture of the way microbes defend themselves against chemical threats in their environment. └

CROSS POLLINATION

It seems that these defense mechanisms are strangely similar across many kinds of organisms -- and many threats. "The issue of resistance is converging from the human infectious disease and agricultural angles," says plant pathologist Jo Handelsman, "whether the microbe is trying to protect itself against antibiotics, fungicides, insecticides, herbicides, even antiviral agents." Handelsman, who studies the interaction of fungi and bacteria at the University of Wisconsin-Madison, points to more similarities. "At the molecular level, there are only a few mechanisms of resistance: change the target molecule, inactivate or decompose the drug or pesticide, sequester (defined) the drug or pesticide, or keep it out of the cell" to begin with.

Let me see your sources

All in all, it makes sense that microbes would have defenses. After all, during their billions of years on the planet, they've overcome countless chemical hazards. But what is the source of the antibiotic resistance genes in the first place?

Probably the organisms that originally produced the antibiotics.

While this might sound odd, it's logical. Assume that I, a lowly bacterium, make some kind of chemical that, say, destroys bacterial cell walls. Wouldn't I need some kind of chemical defense against what kids sometime call "my own medicine?"

This supposition is not only logical, it may even be true, says Davies. "We find resistance genes in the streptomycetes (bacteria that produce many antibiotics) that have exactly the same biochemical function as the resistance genes" in samples from hospital patients. And since the gene sequences are similar -- but not identical -- it's tempting to think that the genes jumped between species, although Davies admits "we can't yet prove it."

Jumping genes

Salyers, who studies this process of gene jumping between species, says bacteria have many tricks for moving resistance genes. For one thing, they seem to be able to cause other bacteria to start genetic swap meets: When a DNA resistance plasmid released by a bacterium is accepted by another bacterium, the recipient may be stimulated to release its own plasmid, a process called retrotransfer. "This transfer capability gives bacteria the ability to sample DNA from other bacteria," Salyers says. To her, the relationship represents a new form of symbiosis (defined).

As if this prospect of bacteria ganging up to defeat antibiotics were not alarming enough, recognize that this generosity extends beyond members of their own species, Salyers says. "Just about any bacterium can get genes from just about any other bacterium."

What is the evidence for this movement? Scientists are finding distantly related bacteria with resistance genes whose DNA sequences (defined) are 95 to 99 percent identical. Although it's extremely improbable by chance alone, it's a strong suggestion -- but not proof -- that the genes have a common origin.

But don't forget that the bacterial anti-antibiotic toolkit also includes multiple mutations, which could explain what's happened in New York City, where a deadly drug-resistant tuberculosis has been on the rampage.

Ancient killer on the rebound

Once upon a time, tuberculosis -- a bacterial infection of the lungs and occasionally other body parts -- was highly responsive to antibiotics. No longer.

TB remains a global menace, afflicting 7.5 million people, according to the World Health Organization, and killing as many as 2.5 million people each year. That makes it the leading cause of death among infectious diseases. TB is particularly severe in AIDS patients, those who can't afford medical care, and patients who disobey doctors. According to the WHO, the pathogen infects one-third of all humans.

Perhaps most ominous, some strains of the disease-causing organism, Mycobacterium tuberculosis, have become resistant to a series of antibiotics. So now just having enough money to buy antibiotics no longer guarantees a cure.

New York City is the epicenter of the TB infection, with 17 percent of the national cases in 1992. In 1992, Harlem had a TB rate of 222 per 100,000 people, more than 20 times the U.S. average. New York is also headquarters of the drug resistance problem, with 61 percent of the national caseload in 1991.

The root of the problem

The problem was that patients were not taking their medicine, says Frantz Medard, director of the TB program at Harlem Hospital. The treatment period ranges from six months -- for an otherwise healthy person with a bug susceptible to antibiotic -- to two years for an AIDS patient. Yet it's very clear that a proper course of treatment can cure the disease, experts say.

Ironically enough, effective treatment is a major cause of the resistance problem, he says. "Within two months, the patient will start feeling well, and stop taking the drugs. But that just causes more problems, because it offers the organism a chance to have the emergence of multi-drug resistance." As the pathogen randomly mutates, the presence of the antibiotic puts selective pressure on it, allowing only the resistant forms to survive. Indeed, it may mutate several times in several places, thus gaining multiple resistance. And anyone who is infected with this strain starts off with an antibiotic-resistant disease.

Furthermore, TB is essentially a disease of poverty, which, at Harlem Hospital, means many patients have AIDS, drug addiction or are homeless. People with these problems, Medard says, "have different priorities, and their health may come last."

The frightening rise in drug-resistant TB in New York City in the early 1990s spurred the city to develop a program called "directly observed therapy," or DOT. Essentially, the idea is not to hand out the drugs, but to watch patients take them. To make the program more humane and effective, Harlem Hospital uses a "family model" of treatment. "Patients are embraced by the staff, they are respected," Medard says. Presents for birthdays and celebrations for patients who haven't missed a dose help boost morale and the success rate. And how does it work? According to research published in 1996 (see "Directly Observed Therapy for Tuberculosis: The Harlem Hospital Experience" in the bibliography) patients made 91 percent of their visits, and 88 percent completed the therapy (as compared to just 11 percent in an unobserved therapy study from the late 1980s). Although New York's epidemic has abated, about 5 percent of patients at Harlem Hospital have drug-resistant TB, and about 2 to 3 percent have strains that are resistant to several drugs.

The slow decline in New York's TB rate is entirely due to the establishment of DOT clinics, Medard says, adding that success is not a reason to discontinue funding, but rather a reason to continue it.

The larger picture

But can countries with less money for health programs use this relatively expensive technique for curing tuberculosis and preventing the emergence of drug-resistant strains? Surprisingly, the "watch-them-gobble-the-pills" technique has worked well in rural South Africa. In the hilly region where the test was done, 58 percent of TB patients also were infected with HIV, the AIDS virus. The treatment supervisors were entrusted with delivering

the twice-weekly dose during the six-month course of treatment. Some of the supervisors were clinic staffers, more were shopkeepers.

At the end of the four-year study, 85 percent of the 1,967 patients who survived had completed treatment, a strong testimony to the ability of rural shopkeepers and health workers to bring the therapy to the patient. (See "Directly Observed Therapy for Tuberculosis in Rural South Africa" and "Tuberculosis Control in Resource-Poor Settings" in the bibliography).

Want to look at a picture of the flu virus.
Is there a way to fix the antibiotic resistance problem before some little bug **fixes us**?

Partial solutions are better than none
Infectious disease specialists are hoping that new attention to the problem will lead to changes that slow the inevitable rise of resistance. The general prescription for controlling the problem includes changes in medical behavior to protect the power of existing anti-microbial weapons, increased research to find new killers for the little infectious killers, and reductions in non-medical uses.

An ounce of prevention

The basic rule is to avoid using antibiotics unnecessarily. Although that's a decision for doctors, patients who implore physicians to treat viral diseases like the common cold with antibiotics are not doing themselves any favors, since antibiotics are worthless against viruses. Presently, there are no national guidelines for using antibiotics.

Says microbiologist Julian Davies of the University of British Columbia, "It's largely left to the physician, who decides whether an antibiotic is given." The American Medical Association has proposed a combination of responses, including education of physicians and patients and more vigorous drug development. But it does not favor national standards on medical practice. Here's how resistance can arise in places where antibiotic usage is uncontrolled.

A pound of cure

Take your meds until the bottle is empty, or however long your doctor specifies. "If you have leftover antibiotic in your medicine chest, you're part of the antibiotic problem," says Barry Kreiswirth, head of the TB program at the Public Health Research Institute in New York City. His reasoning? Many people quit taking the drugs after the symptoms of their infection have disappeared, but some partly-resistant microbes might remain. If you quit taking your meds at that point, you're allowing the partly-resistant organisms to survive and multiply. It's the same dynamic with TB -- but with "tragic consequences," he says.

Be specific

Use the most specific antibiotic possible. Targeted, or "narrow-spectrum," antibiotics will kill the offending bug without sparking resistance among other bacteria living in the patient, as broader-spectrum drugs might. This would call for greater use of susceptibility testing -- exposing colonies of human pathogen to various antibiotics to see which kill the bacteria. (Alarmed that you might be carrying other bacteria? Don't be. The human gut is a veritable zoo of bacteria -- most are helpful, and many are essential for life. In fact, in terms of cells, your own body cells are outnumbered by the bacterial cells you carry, mainly in the gut.)

Be logical

Use the common antibiotics first. If they work, there will be no need to expose the bugs to more exotic drugs, which serve as a second line of defense.

Reduce hospital-transmitted infections

Improve infection control in hospitals. In other words, kill the bugs before they get inside patients. That can be done with ultraviolet lights, better sanitation, and putting patients with recalcitrant infections in isolation wards. One example of how this would work was a recent experiment by Dennis Maki, a University of Wisconsin Hospital specialist in hospital-transmitted infections, who showed that coating intravenous catheters with antiseptic reduced infections by 80 percent.

New drugs

Invent antibiotics that have new mechanisms for killing microbes. Ideally, notes Kreiswirth, two new drugs could be used at once, to slow the development of resistance. The Why Files discussed the evolution of microbial resistance in the context of HIV and AIDS. Find drugs that improve the action of existing antibiotics.

New vaccines

Invent vaccines against common microbial diseases to prevent infection in the first place. Although vaccines make people immune to specific diseases and eliminate the need for drug treatment, Kreiswirth says they aren't perfect: "People don't take vaccines today," he notes. Many elderly people who could benefit from flu shots don't get them, and "measles spreads like wildfire" among the Amish, who refuse vaccination.

Reduce widespread use

Consider reducing the widespread use of antibiotics in animal feeds. "There are real questions about whether we should be feeding antibiotics to animals and spraying them on fruit trees to prevent rot," says Abigail Salyers, a microbiologist at the University of Illinois. But what seems like a good idea is, she admits, not backed up by much evidence -- either way.

Reality check

Is this reality, or is this overkill? Use aTelecondom "in the operational mode."

Realistically speaking

These measures might go a long way toward preserving the life-giving gift of antibiotics, but most experts figure the bugs will win in the end. It's not just that single-celled organisms have been around since the dawn of life -- more than three billion years back. It's also their huge numbers, their short generation times, and their ability to swap genes that makes them so flexible and dangerous. "There's no ultimate solution to the antibiotic resistance problem," says Davies. "Microbes will always become resistant to agents that are put out to kill them. It's a fact of life. But we, as intelligent people, can slow that down."

Indeed, the important infectious diseases are not medical problems so much as social ones, Kreiswirth argues. AIDS, after all, is entirely preventable by changes in behavior. And if you get TB "because the guy next door did a bad job of treating himself," he says, "that's bad luck." But by refusing to take his medicines until it killed the bacterium, "the guy next door has had a failure of personal and social responsibility."

If you've reached this far in the article, it's important to stress that, while we've offered some speculation about the mechanisms that cause antibiotic resistance, the actual problem is not speculation, not theory. According to Kreiswirth, some strains of TB now in New York City and elsewhere are resistant to as many as nine drugs. "We've reached the point where some cases of TB are essentially untreatable."

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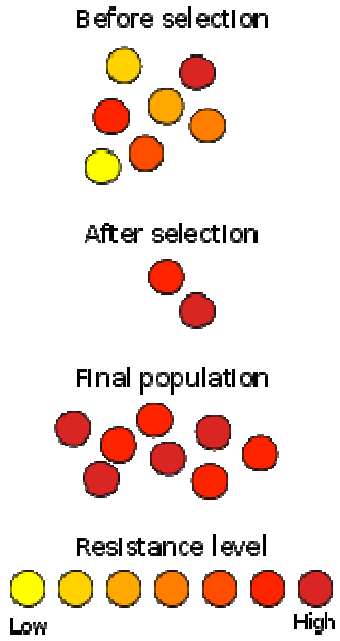
ANTIBIOTIC RESISTANCE

Wikipedia

http://en.wikipedia.org/wiki/Antibiotic_resistance

Antibiotic resistance is the ability of a microorganism to withstand the effects of antibiotics. It is a specific type of drug resistance. Antibiotic resistance evolves via natural selection acting upon random mutation, but it can also be engineered by applying an evolutionary stress on a population. Once such a gene is generated, bacteria can then transfer the genetic information in a horizontal fashion (between individuals) by plasmid exchange. If a bacterium carries several resistance genes, it is called **multiresistant** or, informally, a **superbug**. The term**antimicrobial resistance** is sometimes used to explicitly encompass organisms other than bacteria. Antibiotic resistance can also be introduced artificially into a microorganism through transformation protocols. This can aid in implanting artificial genes into the microorganism. If the resistance gene is linked with the gene to

be implanted, the antibiotic can be used to kill off organisms that lack the new gene. **[edit]Causes and risk factors**



Schematic representation of how antibiotic resistance evolves via natural selection. The top section represents a population of bacteria before exposure to an antibiotic. The middle section shows the population directly after exposure, the phase in which selection took place. The last section shows the distribution of resistance in a new generation of bacteria. The legend indicates the resistance levels of individuals.

Antibiotic resistance can be a result of horizontal gene transfer,[1] and also of unlinked point mutations in the pathogen genome and a rate of about 1 in 10^8 per chromosomal replication. The antibiotic action against the pathogen can be seen as an environmental pressure; those bacteria which have a mutation allowing them to survive will live on to reproduce. They will then pass this trait to their offspring, which will result in a fully resistant colony.

Several studies have demonstrated that patterns of antibiotic usage greatly affect the number of resistant organisms which develop[*citation needed*]. Overuse of broad-spectrum antibiotics, such as second- and third-generation cephalosporins, greatly hastens the development of **methicillin**resistance. Other factors contributing towards resistance include incorrect diagnosis, unnecessary prescriptions, improper use of antibiotics by patients, the impregnation of household items and children's toys with low levels of antibiotics, and the administration of antibiotics by mouth in livestock for growth promotion. Also unsound practices in the pharmaceutical manufacturing industry can contribute towards the likelihood of creating antibiotic resistant strains. [2]

Researchers have recently demonstrated the bacterial protein LexA may play a key role in the acquisition of bacterial mutations.[3]

[edit]Mechanisms

The four main mechanisms by which microorganisms exhibit resistance to antimicrobials are:

Drug inactivation or modification: e.g. enzymatic deactivation of *Penicillin* G in some penicillin-resistant bacteria through the production of β-lactamases.

Alteration of target site: e.g. alteration of PBP—the binding target site of penicillins—in MRSA and other penicillin-resistant bacteria.

Alteration of metabolic pathway: e.g. 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. Instead, like mammalian cells, they turn to utilizing preformed folic acid.

Reduced drug accumulation: by decreasing drug permeability and/or increasing active efflux (pumping out) of the drugs across the cell surface.[4]

There are three known mechanisms of fluoroquinolone resistance. Some types of efflux pumps 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.[5]

[edit]Resistant pathogens

[edit]*Staphylococcus aureus*

Staphylococcus aureus (colloquially known as "Staph aureus" or a *Staph infection*) is one of the major resistant pathogens. Found on the mucous membranes and the skin of around a third of the population, it is extremely adaptable to antibiotic pressure. It was the first bacterium in which penicillin resistance was found—in 1947, just four years after the drug started being mass-produced. Methicillin was then the antibiotic of choice, but has since been replaced by oxacillin due to significant kidney toxicity. MRSA (methicillin-resistant *Staphylococcus aureus*) was first detected in Britain in 1961 and is now "quite common" in hospitals. MRSA was responsible for 37% of fatal cases of blood poisoning in the UK in 1999, up from 4% in 1991. Half of all *S. aureus* infections in the US are resistant to penicillin, methicillin, tetracycline and erythromycin.

This left vancomycin as the only effective agent available at the time. However, strains with intermediate (4-8 ug/ml) levels of resistance, termed GISA (glycopeptide intermediate*Staphylococcus aureus*) or VISA (vancomycin intermediate *Staphylococcus aureus*), began appearing in the late 1990s. The first identified case was in Japan in 1996, and strains have since been found in hospitals in England, France and the US. The first documented strain with complete (>16 ug/ml) resistance to vancomycin, termed VRSA (Vancomycin-resistant*Staphylococcus aureus*) appeared in the United States in 2002.

A *new* class of antibiotics, oxazolidinones, became available in the 1990s, and the first commercially available oxazolidinone, linezolid, is comparable to vancomycin in effectiveness against MRSA. Linezolid-resistance in *Staphylococcus aureus* was reported in 2003.

CA-MRSA (Community-acquired MRSA) has now emerged as an epidemic that is responsible for rapidly progressive, fatal diseases including necrotizing pneumonia, severe sepsis andnecrotizing fasciitis.[6] Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most frequently identified antimicrobial drug-resistant pathogen in US hospitals. The epidemiology of infections caused by MRSA is rapidly changing. In the past 10 years, infections caused by this organism have emerged in the community. The 2 MRSA clones in the United States most closely associated with community outbreaks, USA400 (MW2 strain, ST1 lineage) and USA300, often contain Panton-Valentine leukocidin (PVL) genes and, more frequently, have been associated with skin and soft tissue infections. Outbreaks of community-associated (CA)-MRSA infections have been reported in correctional facilities, among athletic teams, among military recruits, in newborn nurseries, and among active homosexual men. CA-MRSA infections now appear to be endemic in many urban regions and cause most CA-S. aureus infections.[7]

[edit]*Streptococcus* and *Enterococcus*

Streptococcus pyogenes (Group A Streptococcus: GAS) infections can usually be treated with many different antibiotics. Early treatment may reduce the risk of death from invasive group A streptococcal disease. However, even the best medical care does not prevent death in every case. For those with very severe illness, supportive care in an intensive care unit may be needed. For persons with necrotizing fasciitis, surgery often is needed to remove damaged tissue.[8] Strains of *S. pyogenes* resistant to macrolide antibiotics have emerged, however all strains remain uniformly sensitive to penicillin.[9]

Resistance of *Streptococcus pneumoniae* to penicillin and other beta-lactams is increasing worldwide. The major mechanism of resistance involves the introduction of mutations in genes encoding penicillin-binding proteins. Selective pressure is thought to play an important role, and use of beta-lactam antibiotics has been implicated as a risk factor for infection and colonization. Streptococcus pneumoniae is responsible for pneumonia, bacteremia, otitis media, meningitis, sinusitis, peritonitis and arthritis.[9]

Penicillin-resistant pneumonia caused by *Streptococcus pneumoniae* (commonly known as *pneumococcus*), was first detected in 1967, as was penicillin-resistant gonorrhea. Resistance to penicillin substitutes is also known as beyond *S. aureus*. By 1993 *Escherichia coli* was resistant to five fluoroquinolone variants. *Mycobacterium tuberculosis* is commonly resistant toisoniazid and rifampin and sometimes universally resistant to the common treatments. Other pathogens showing some resistance include *Salmonella*, *Campylobacter*, and *Streptococci*. *Enterococcus faecium* is another superbug found in hospitals. Penicillin-Resistant Enterococcus was seen in 1983, vancomycin-resistant enterococcus (VRE) in 1987, and Linezolid-Resistant Enterococcus (LRE) in the late 1990s.

[edit]*Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a highly prelevant opportunistic pathogen. One of the most worrisome characteristics of *P. aeruginosa* consists in its low antibiotic susceptibility. This low susceptibility is attributable to a concerted action of multidrug efflux pumps with chromosomally-encoded antibiotic resistance genes (e.g. *mexAB-oprM*, *mexXY* etc) and the low permeability of the bacterial cellular envelopes. Besides intrinsic resistance, *P. aeruginosa* easily develop acquired resistance either by mutation in chromosomally-encoded genes, or by the horizontal gene transfer of antibiotic resistance determinants. Development of multidrug resistance by *P. aeruginosa* isolates requires several different genetic events that include acquisition of different mutations and/or horizontal transfer of antibiotic resistance genes. Hypermutation favours the selection of mutation-driven antibiotic resistance in *P. aeruginosa*strains producing chronic infections, whereas the clustering of several different antibiotic resistance genes in integrons favours the concerted acquisition of antibiotic resistance determinants. Some recent studies have shown that phenotypic resistance associated to biofilm formation or to the emergence of small-colony-variants may be important in the response of*P. aeruginosa* populations to antibiotics treatment.[10]

[edit]*Clostridium difficile*

Clostridium difficile is a nosocomial pathogen that causes diarrheal disease in hospitals world wide.[11][12] Clindamycin-resistant *C. difficile* was reported as the causative agent of large outbreaks of diarrheal disease in hospitals in New York, Arizona, Florida and Massachusetts between 1989 and 1992.[13] Geographically dispersed outbreaks of *C. difficile* strains resistant to fluoroquinolone antibiotics, such as Cipro (ciprofloxacin) and Levaquin (levofloxacin), were also reported in North America in 2005.[14]

[edit]*Salmonella* and *E. coli*

E. coli and Salmonella come directly from contaminated food. Of the meat that is contaminated with E. coli, eighty percent of the bacteria are resistant to one or more drugs made; it causes bladder infections that are resistant to antibiotics ("HSUS Fact Sheet"). Salmonella was first found in humans in the 1970s and in some cases is resistant to as many as nine different antibiotics ("HSUS Fact Sheet"). When both bacterium are spread, serious

health conditions arise. Many people are hospitalized each year after becoming infected, and some die as a result.

[edit]*Acinetobacter baumannii*

On the 5th November 2004 , the Centers for Disease Control and Prevention (CDC) reported an increasing number of *Acinetobacter baumannii* bloodstream infections in patients at military medical facilities in which service members injured in the Iraq/Kuwait region during Operation Iraqi Freedom and in Afghanistan during Operation Enduring Freedom were treated. Most of these showed multidrug resistance (MRAB), with a few isolates resistant to all drugs tested.[15][16]

[edit]Role of animals

Methicillin Resistant Staphylococcus Aureus (MRSA) is acknowledged to be a human commensal and pathogen. MRSA has been found in cats, dogs and horses, where it can cause the same problems as it does in humans. Owners can transfer the organism to their pets and vice-versa, and MRSA in animals is generally believed to be derived from humans.

The United States Food and Drug Administration has responsibility for determining the safety of food as well as drugs. Drugs are frequently used for animals the same way they are used in people – to treat illness and improve the health of the animals. Drugs are used in animals that are used as human food, such as cows, pigs, chickens, fish, etc., and these drugs can affect the safety of the meat, milk, and eggs produced from those animals. Therefore, FDA has the responsibility to review drugs intended for use in food animals, and to be sure that the use of the drugs does not result in harmful residues in food or create resistant pathogens that can harm human health. For example, farm animals, particularly pigs, are believed to be able to infect people with MRSA.[17] In 1951, the FDA approved the use of antibiotics in animal feed without a veterinary medical prescription; Concerns about resistance have been revisited several times since then, and most antimicrobials have not been shown to be a hazard. Europe quickly followed suit. As the spread of drug-resistant bacteria became a concern, countries began questioning the practice. In 1969, Britain issued the Swann Report,[18] which recommended that human therapeutic antibiotics be banned from being used as growth promoters in agriculture. The report was largely ignored. It's pointed out by industry, that most of the routine feed drugs are either not used in human medicine, or are older compounds that have long been superseded by later-generation drugs.

Nearly 30 years later, the World Health Organization concluded that antibiotics as growth promoters in animal feeds should be prohibited (in the absence of risk assessments). And in 1998, European Union health ministers voted to ban four antibiotics widely used to promote animal growth (despite their scientific panel's recommendations). Regulation banning the use of antibiotics in European feed, with the exception of two antibiotics in poultry feeds, became effective in 2006.[19] With good animal husbandry and hygiene, there

shouldn't be adverse effects, health-wise or production-wise, from not using antibiotics in animal feed. In Scandinavia, there's evidence that the ban has led to a lower prevalence of antimicrobial resistance in (non-hazardous) animal bacterial populations.[20] Meanwhile, in the poultry industry, the ban hasn't had a deleterious effect. Economic performance in poultry production wasn't adversely affected either. Whether banning feed drugs has had any actual benefit to public health has been the topic of several reviews. Foodborne incidence and resistance patterns in humans, have not declined in countries featuring animal bans, in fact some have increased. Meanwhile, there were higher mortality in swine populations following bans. The "success" of Scandinavain and EU bans is therefore highly questionable as a useful policy, according to several published reviews. In the United States, antibiotic use in animal feeds remains controversial, due to a well-financed anti-agricultural campaign.[*citation needed*] The FDA first called for restrictions in 1997,[21] which generated many studies and reports on the issue. In 1980, the Institute of Medicine reviewed the subject and recommended that more studies be conducted.[22] In 1999, the General Accounting Office (GAO) also concluded that the evidence was inconclusive. A follow-up 2004 GAO study[23] found that evidence existed of antibiotic-resistant bacteria being transferred from animals to humans. But since federal agencies don't collect data on antibiotic use in animals, conclusions on the potential impact on human health couldn't be made. Therefore, antibiotics are still used in U.S. animal feed—along with evidence of other worrisome ingredients.[24][25]

Growing U.S. consumer concern about using antibiotics in animal feed has led to a niche market of "antibiotic-free" animal products, but this small market is unlikely to change entrenched industry-wide practices.[26] Within FDA, the animal drug review duties have been assigned to one of the Agency's operating units, the Center for Veterinary Medicine. Their guidance is used to evaluate all types and uses of antimicrobials, including what some refer to as **subtherapeutic use**. Although that term has not been defined by regulation, **it describes the use of a product to boost an animal's ability to grow and produce more food, instead of treating or preventing an infectious disease.** It could also be used to evaluate antimicrobials if they are used for growth promotion, and for antimicrobials that are products of genetic engineering. Antimicrobials are used with animals that we use to produce food for human consumption, including cows (for beef and milk production), pigs, chickens, turkeys, fish, and sheep, to increase production. **Antimicrobials are used in feeds for some species**, and the animals fed the antimicrobial feeds often grow faster while consuming less feed than animals not given antimicrobials in feed**. In addition to determining whether the use of a drug would result in residues left in the meat, milk, or eggs, FDA must ensure that the use of antimicrobials in food-producing animals does not lead to the development of resistant bacteria that can become a public health concern.** This document[*clarification needed*] is one way that drug sponsors can submit information that address the issue of the microbial safety of antimicrobial new animal drugs. A sponsor is free to use other scientifically valid approaches to demonstrate the safety of their proposed product. CVM first said in December 1999 that it would consider the question of the fostering of antimicrobial resistance when reviewing antimicrobials for use in animals. That announcement was followed a year later with what was called FDA's "Framework Document," which first described the FDA's plan to use risk

assessments of the development of antimicrobial resistance in determining the safety of antimicrobials for food-producing animals. The guidance document was first published as a draft in September 2002, to allow the scientific community to comment on the concept and on the science FDA used to develop the guidance document. The FDA allows the use of antimicrobials because they are a valuable tool that veterinarians can use to treat sick animals, and so livestock producers can use antimicrobials to produce meat, milk, and eggs more efficiently.

In 2001, the Union of Concerned Scientists estimated that greater than 70% of the antibiotics used in the US are given to food animals (e.g. chickens, pigs and cattle) in the absence of disease.[27] This 2001 report, however, has been shown to over-estimate animal usage rates. Antibiotic use in food animal production has been associated with the emergence of antibiotic-resistant strains of bacteria including Salmonella, Campylobacter, Escherichia coli and Enterococcus, among others. There is substantial evidence from the US and European Union that these resistant bacteria cause antibiotic-resistant infections in humans[*citation needed*]. The American Society for Microbiology (ASM)[*citation needed*], the American Public Health Association(APHA) and the American Medical Association (AMA) have called for substantial restrictions on antibiotic use in food animal production including an end to all "non-therapeutic" uses. The food animal and pharmaceutical industries have fought hard to prevent new regulations that would limit the use of antibiotics in food animal production, pointing out that while concerns exist, risk assessments and actual data have demonstrated little to no risk in this area. For example, in 2000 the US Food and Drug Administration (FDA) announced their intention to rescind approval for fluoroquinolone use in poultry production because of substantial evidence linking it to the emergence of fluoroquinolone resistant Campylobacter infections in humans. The final decision to ban fluoroquinolones from use in poultry production was not made until 5 years later because of challenges from the food animal and pharmaceutical industries.[28] Today, there are two federal bills (S. 549[29] and H.R. 962[30]) aimed at phasing out "non-therapeutic" antibiotics in US food animal production. These bills are nominally endorsed by many public health and medical organizations including the American Nurses Association (ANA))[*citation needed*], the American Academy of Pediatrics (AAP)[*citation needed*], and the American Public Health Association (APHA)[*citation needed*]. Other professional groups, notably animal science, food science, veterinary, and industry groups do not support this legislation, however, pointing out that current uses are not shown to be hazardous and have legitimate disease prevention roles.

[edit]Alternatives

[edit]Prevention

Rational use of antibiotics may reduce the chances of development of opportunistic infection by antibiotic-resistant bacteria due to dysbacteriosis. In one study the use of fluoroquinolones are clearly associated with *Clostridium difficile* infection, which is a leading cause of nosocomial diarrhea in the United States,[31] and a major cause of death, worldwide.[32]

There is clinical evidence that topical dermatological preparations containing tea tree oil and thyme oil may be effective in preventing transmittal of CA-MRSA. [33]
Vaccines do not suffer the problem of resistance because a vaccine enhances the body's natural defenses, while an antibiotic operates separately from the body's normal defenses. Nevertheless, new strains may evolve that escape immunity induced by vaccines.

While theoretically promising, anti-staphylococcal vaccines have shown limited efficacy, because of immunological variation between *Staphylococcus* species, and the limited duration of effectiveness of the antibodies produced. Development and testing of more effective vaccines is under way.

The Commonwealth Scientific and Industrial Research Organization (CSIRO), realizing the need for the reduction of antibiotic use, has been working on two alternatives. One alternative is to prevent diseases by adding [cytokine]s instead of antibiotics to animal feed. These proteins are made in the animal body "naturally" after a disease and are not antibiotics so they do not contribute to the antibiotic resistance problem. Furthermore, studies on using cytokines have shown that they also enhance the growth of animals like the antibiotics now used, but without the drawbacks of non-therapeutic antibiotic use. Cytokines have the potential to achieve the animal growth rates traditionally sought by the use of antibiotics without the contribution of antibiotic resistance associated with the widespread non-therapeutic uses of antibiotics currently utilized in the food animal production industries. Additionally, CSIRO is working on vaccines for diseases.

[edit]Phage therapy
Phage therapy, an approach that has been extensively researched and utilized as a therapeutic agent for over 60 years, especially in the Soviet Union, is an alternative that might help with the problem of resistance. Phage therapy was widely used in the United States until the discovery of antibiotics, in the early 1940s. Bacteriophages or "phages" are viruses that invade bacterial cells and, in the case of lytic phages, disrupt bacterial metabolism and cause the bacterium to lyse. Phage therapy is the therapeutic use of lytic bacteriophages to treatpathogenic bacterial infections.[34][35][36]

Bacteriophage therapy is an important alternative to antibiotics in the current era of multidrug resistant pathogens. A review of studies that dealt with the therapeutic use of phages from 1966–1996 and few latest ongoing phage therapy projects via internet showed: phages were used topically, orally or systemically in Polish and Soviet studies. The success rate found in these studies was 80–95% with few gastrointestinal or allergic side effects. British studies also demonstrated significant efficacy of phages against *Escherichia coli*, *Acinetobacter* spp.,*Pseudomonas* spp and *Staphylococcus aureus*. US studies dealt with improving the bioavailability of phage. Phage therapy may prove as an important alternative to antibiotics for treating multidrug resistant pathogens.[37][38]

[edit]Development of new drugs

Until recently, research and development (R&D) efforts have provided new drugs in time to treat bacteria that became resistant to older antibiotics. That is no longer the case. The potential crisis at hand is the result of a marked decrease in industry R&D, and the increasing prevalence of resistant bacteria. Infectious disease physicians are alarmed by the prospect that effective antibiotics may not be available to treat seriously ill patients in the near future.

The pipeline of new antibiotics is drying up. Major pharmaceutical companies are losing interest in the antibiotics market because these drugs may not be as profitable as drugs that treat chronic (long-term) conditions and lifestyle issues.[39]

The resistance problem demands that a renewed effort be made to seek antibacterial agents effective against pathogenic bacteria resistant to current antibiotics. One of the possible strategies towards this objective is the rational localization of bioactive phytochemicals. Plants have an almost limitless ability to synthesize aromatic substances, most of which arephenols or their oxygen-substituted derivatives such as tannins. Most are secondary metabolites, of which at least 12,000 have been isolated, a number estimated to be less than 10% of the total[*citation needed*]. In many cases, these substances serve as plant defense mechanisms against predation by microorganisms, insects, and herbivores. Many of the herbs and spices used by humans to season food yield useful medicinal compounds including those having antibacterial activity.[40][41][42]
Traditional healers have long used plants to prevent or cure infectious conditions. Many of these plants have been investigated scientifically for antimicrobial activity and a large number of plant products have been shown to inhibit growth of pathogenic bacteria. A number of these agents appear to have structures and modes of action that are distinct from those of the antibiotics in current use, suggesting that cross-resistance with agents already in use may be minimal. For example the combination of 5'-methoxyhydnocarpine and berberine in herbs likeHydrastis canadensis and Berberis vulgaris can block the MDR-pumps that cause multidrug resistance. This has been shown for Staphylococcus aureus.[43]

Archaeocins is the name given to a new class of potentially useful antibiotics that are derived from the Archaea group of organisms. Eight archaeocins have been partially or fully characterized, but hundreds of archaeocins are believed to exist, especially within the haloarchaea. The prevalence of archaeocins is unknown simply because no one has looked for them. The discovery of new archaeocins hinges on recovery and cultivation of archaeal organisms from the environment. For example, samples from a novel hypersaline field site, Wilson Hot Springs, recovered 350 halophilic organisms; preliminary analysis of 75 isolates showed that 48 were archaeal and 27 were bacterial.[44]

In research published on October 17, 2008 in *Cell*, a team of scientists pinpointed the place on bacteria where the antibiotic myxopyronin launches its attack, and why that attack is successful. The myxopyronin binds to and inhibits the crucial bacterial enzyme, RNA polymerase. The myxopyronin changes the structure of the switch-2 segment of the enzyme, inhibiting its function of reading and transmitting DNA code. This prevents RNA polymerase from delivering genetic information to the ribosomes, causing the bacteria to die.[45]
One of the major causes of antibiotic resistance is the decrease of effective drug concentrations at their target place, due to the increased action of ABC transporters. Since ABC transporter blockers can be used in combination with current drugs to increase their effective intracellular concentration, the possible impact of ABC transporter inhibitors is of great clinical interest. ABC transporter blockers that may be useful to increase the efficacy of current drugs have entered clinical trials and are available to be used in therapeutic regimes.[4]

[edit]Applications

Antibiotic resistance is an important tool for genetic engineering. By constructing a plasmid which contains an antibiotic resistance gene as well as the gene being engineered or expressed, a researcher can ensure that when bacteria replicate, only the copies which carry along the plasmid survive. This ensures that the gene being manipulated passes along when the bacteria replicates.

The most commonly used antibiotics in genetic engineering are generally "older" antibiotics which have largely fallen out of use in clinical practice. These include:
ampicillin
kanamycin
tetracycline
chloramphenicol
Industrially the use of antibiotic resistance is disfavored since maintaining bacterial cultures would require feeding them large quantities of antibiotics. Instead, the use of auxotrophicbacterial strains (and function-replacement plasmids) is preferred.

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BACTERIAL RESISTANCE TO ANTIBIOTICS

Todar's Online Textbook of Bacteriology
http://www.textbookofbacteriology.net/resantimicrobial.html

Introduction

In the past 60 years, antibiotics have been critical in the fight against infectious disease caused by bacteria and other microbes. Antimicrobial chemotherapy has been a leading cause for the dramatic rise of average life

expectancy in the Twentieth Century. However, disease-causing microbes that have become resistant to antibiotic drug therapy are an increasing public health problem. Wound infections, gonorrhea, tuberculosis, pneumonia, septicemia and childhood ear infections are just a few of the diseases that have become hard to treat with antibiotics. One part of the problem is that bacteria and other microbes that cause infections are remarkably resilient and have developed several ways to resist antibiotics and other antimicrobial drugs. Another part of the problem is due to increasing use, and misuse, of existing antibiotics in human and veterinary medicine and in agriculture.

In 1998, in the United States, 80 million prescriptions of antibiotics for human use were filled. This equals 12,500 tons in one year. Animal and agricultural uses of antibiotics are added to human use. Agricultural practices account for over 60% of antibiotic usage in the U.S., so this adds an additional 18,000 tons per year to the antibiotic burden in the environment.

Nowadays, about 70 percent of the bacteria that cause infections in hospitals are resistant to at least one of the drugs most commonly used for treatment. Some organisms are resistant to all approved antibiotics and can only be treated with experimental and potentially toxic drugs. An alarming increase in resistance of bacteria that cause community acquired infections has also been documented, especially in the staphylococci and pneumococci (*Streptococcus pneumoniae)*, which are prevalent causes of disease and mortality. In a recent study, 25% of bacterial pneumonia cases were shown to be resistant to penicillin, and an additional 25% of cases were resistant to more than one antibiotic.

Microbial development of resistance, as well as economic incentives, has resulted in research and development in the search for new antibiotics in order to maintain a pool of effective drugs at all times. While the development of resistant strains is inevitable, the slack ways that we administer and use antibiotics has greatly exacerbated the process.

Unless antibiotic resistance problems are detected as they emerge, and actions are taken immediately to contain them, society could be faced with previously treatable diseases that have become again untreatable, as in the days before antibiotics were developed.

History of antibiotics and emergence of antibiotic resistance

The first antibiotic, penicillin, was discovered in 1929 by Sir Alexander Fleming, who observed inhibition of staphylococci on an agar plate contaminated by a *Penicillium* mold. Fleming was searching for potential antibacterial compounds. He noticed that a patch of the mold *Penicillium notatum* had grown on a plate containing the bacterium *Staphylococcus* and that around the mold there was a zone where no *Staphylococcus* could grow. After more research, he was able to show that culture broth of the mold

prevented growth of the *Staphylococcus*even when diluted up to 800 times. He named the active substance penicillin but was unable to isolate it.

In the center of the plate is a colony of *Penicillium notatum,* a mold that produces penicillin. After appearance of the mold colony, the plate was overlaid with a bacterial culture of *Micrococcus luteus* which forms a yellow "lawn" of growth. A zone of inhibition of bacterial growth surrounds the fungal colony where penicillin has diffused into the medium.

Several years later, in 1939, Ernst Chain and Howard Florey developed a way to isolate penicillin and used it to treat bacterial infections during the Second World War. The new drug came into clinical usage in 1946 and made a huge impact on public health. For these discoveries Fleming, Chain and Florey were awarded the Nobel prize in 1945. Their discovery and development revolutionized modern medicine and paved the way for the development of many more natural antibiotics.

While Fleming was working on penicillin, Gerhard Domagk, a German doctor, announced the discovery of a synthetic molecule with antibacterial properties. He named the compound Prontosil, and it became the first of a long series of synthetic antibiotics called sulfonamides or sulfa drugs. Prontosil was introduced to clinical use in the 1930s and was used to combat urinary tract infections, pneumonia and other conditions. While sulfa drugs in many cases are not as effective as natural antibiotics, they are now in widespread use for the treatment of many conditions. Gerhard Domagk was awarded the Nobel prize in 1939 for his discovery of Prontosil.

In 1946, penicillin became generally available for treatment of bacterial infections, especially those caused by staphylococci and streptococci. Initially, the antibiotic was effective against all sorts of infections caused by these two Gram-positive bacteria. Penicillin had unbelievable ability to kill these bacterial pathogens without harming the host that harbored them. It is important to note that a significant fraction of all human infections are caused by these two bacteria (i.e., strep throat, pneumonia, scarlet fever, septicemia, skin infections, wound infections, etc.).

In the late 1940s and early 1950s, new antibiotics were introduced, including streptomycin, chloramphenicol and tetracycline, and the age of antibiotic chemotherapy came into full being. These antibiotics were effective against the full array of bacterial pathogens including Gram-positive and Gram-negative bacteria, intracellular parasites, and the tuberculosis bacillus. Synthetic antimicrobial agents such as the "sulfa drugs" (sulfonamides) and anti-tuberculosis drugs, such as para aminosalicylic acid (PAS) and isoniazid (INH), were also brought into wider usage.

The first signs of antibiotic resistance

There has probably been a gene pool in nature for resistance to antibiotic as long as there has been for antibiotic

production, for most microbes that are antibiotic producers are resistant to their own antibiotic. In retrospect, it is not surprising that resistance to penicillin in some strains of staphylococci was recognized almost immediately after introduction of the drug in 1946. Likewise, very soon after their introduction in the late 1940s, resistance to streptomycin, chloramphenicol and tetracycline was noted. By 1953, during a *Shigella* outbreak in Japan, a strain of the dysentery bacillus (*Shigella dysenteriae*) was isolated which was multiple drug resistant, exhibiting resistance to chloramphenicol, tetracycline, streptomycin and the sulfonamides. Over the years, and continuing into the present almost every known bacterial pathogen has developed resistance to one or more antibiotics in clinical use.

Evidence also began to accumulate that bacteria could pass genes for drug resistance between strains and even between species. For example, antibiotic-resistance genes of staphylococci are carried on plasmids that can be exchanged with *Bacillus, Streptococcus* and *Enterococcus* providing the means for acquiring additional genes and gene combinations. Some are carried on transposons, segments of DNA that can exist either in the chromosome or in plasmids. In any case, it is clear that genes for antibiotic resistance can be exchanged between strains and species of bacteria by means of the processes of horizontal gene transmission (HGT).

Multiple drug resistant organisms

Multiple drug resistant organisms are resistant to treatment with several, often unrelated, antimicrobial agents as described above in *Shigella*. Some of the most important types of multiple drug resistant organisms that have been encountered include:
MRSA - methicillin/oxacillin-resistant *Staphylococcus aureus*
VRE - vancomycin-resistant enterococci
ESBLs - extended-spectrum beta-lactamases (which are resistant to cephalosporins and monobactams)
PRSP - penicillin-resistant *Streptococcus pneumoniae*

MRSA and VRE are the most commonly encountered multiple drug resistant organisms in patients residing in non-hospital healthcare facilities, such as nursing homes and other long-term care facilities. PRSP are more common in patients seeking care in outpatient settings such as physicians' offices and clinics, especially in pediatric settings. ESBLs are most often encountered in the hospital (intensive care) setting, but MRSA and VRE also have a significant nosocomial ecology.

Methicillin-Resistant Staph Aureus. **MRSA** refers to "methicillin-resistant*Staphylococcus aureus*", which are strains of the bacterium that are resistant to the action of methicillin, and related beta-lactam antibiotics (e.g. penicillin and cephalosporin). MRSA have evolved resistance not only to beta-lactam antibiotics, but to several classes of antibiotics. Some MRSA are resistant to all but one or two antibiotics, notably vancomycin-resistant.

But there have been several reports of VRSA (Vancomycin-Resistant Staph Aureus) that are troublesome in the ongoing battle against staph infections.

MRSA are often sub-categorized as Hospital-Associated MRSA (HA-MRSA) or Community-Associated MRSA (CA-MRSA), depending upon the circumstances of acquiring disease. Based on current data, these are distinct strains of the bacterial species.

HA-MRSA occurs most frequently among patients who undergo invasive medical procedures or who have weakened immune systems and are being treated in hospitals and healthcare facilities such as nursing homes and dialysis centers. MRSA in healthcare settings commonly causes serious and potentially life threatening infections, such as bloodstream infections, surgical site infections or pneumonia.

In the case of HA- MRSA, patients who already have an MRSA infection or who carry the bacteria on their bodies but do not have symptoms (colonized) are the most common sources of transmission. The main mode of transmission to other patients is through human hands, especially healthcare workers' hands. Hands may become contaminated with MRSA bacteria by contact with infected or colonized patients. If appropriate hand hygiene such as washing with soap and water or using an alcohol-based hand sanitizer is not performed, the bacteria can be spread when the healthcare worker touches other patients.

MRSA infections that occur in otherwise healthy people who have not been recently (within the past year) hospitalized or had a medical procedure (such as dialysis, surgery, catheters) are categorized as community-associated (CA-MRSA) infections. These infections are usually skin infections, such as abscesses, boils, and other pus-filled lesions.

About 75 percent of CA-MRSA infections are localized to skin and soft tissue and usually can be treated effectively. However, CA-MRSA strains display enhanced virulence, spread more rapidly and cause more severe illness than traditional HA-MRSA infections, and can affect vital organs leading to widespread infection (sepsis), toxic shock syndrome and pneumonia. It is not known why some healthy people develop CA-MRSA skin infections that are treatable whereas others infected with the same strain develop severe, fatal infections.

Studies have shown that rates of CA-MRSA infection are growing fast. One study of children in south Texas found that cases of CA-MRSA had a 14-fold increase between 1999 and 2001.

CA-MRSA skin infections have been identified among certain populations that share close quarters or experience more skin-to-skin contact. Examples are **team athletes, military recruits, and prisoners**. However, more and more CA-MRSA infections are being seen in the general community as well, especially in certain geographic

regions.

Also, CA-MRSA are infecting much younger people. In a study of Minnesotans published in The Journal of the American Medical Association, the average age of people with MRSA in a hospital or healthcare facility was 68. But the average age of a person with CA-MRSA was only 23.

More people in the U.S. now die from MRSA infection than from AIDS. Methicillin-resistant *Staphylococcus aureus* was responsible for an estimated 94,000 life-threatening infections and 18,650 deaths in 2005, as reported by CDC in the Oct. 17, 2007 issue of The Journal of the American Medical Association. The national estimate is more than double the invasive MRSA prevalence reported five years earlier. That same year, roughly 16,000 people in the U.S. died from AIDS, according to CDC. While most invasive MRSA infections could be traced to a hospital stay or some other health care exposure, about 15% of invasive infections occurred in people with no known health care risk. Two-thirds of the 85% of MRSA infections that could be traced to hospital stays or other health care exposures occurred among people who were no longer hospitalized. People over age 65 were four times more likely than the general population to get an MRSA infection. Incidence rates among blacks were twice that of the general population, and rates were lowest among children over the age of 4 and teens.

Extended-Spectrum beta-lactamase (ESBL) - producing Gram-negative bacteria Extended-spectrum beta-lactamases (ESBLs) are plasmid-associated beta lactamases that have recently been found in the *Enterobacteriaceae*. ESBLs are capable of hydrolyzing penicillins, many narrow spectrum cephalosporins, many extended-spectrum cephalosporins, oxyimino-cephalosporins (cefotaxime, ceftazidime), and monobactams (aztreonam). Beta-lactamase inhibitors (e.g. clavulanic acid) generally inhibit ESBL producing strains. ESBL producing isolates are most commonly *Klebsiella ssp*, predominantly *Klebsiella pneumoniae*, and *E. coli*, but they have been found throughout the *Enterobacteriaeae.*

Because ESBL enzymes are plasmid mediated, the genes encoding these enzymes are easily transferable among different bacteria. Most of these plasmids not only contain DNA encoding ESBL enzymes but also carry genes conferring resistance to several non-ß-Lactam antibiotics. Consequently, most ESBL isolates are resistant to many classes of antibiotics. The most frequent coresistances found in ESBL-producing organisms are aminoglycosides, fluoroquinolones, tetracyclines, chloramphenicol, and sulfamethoxazole-trimethoprim. Treatment of these multiple drug-resistant organisms is a therapeutic challenge.

ESBL producing strains have been isolated from abscesses, blood, catheter tips, lung, peritoneal fluid, sputum, and throat cultures. They apparently have a world-wide distribution. Rates of isolation vary greatly worldwide and within geographic areas and are rapidly changing over time. In the United States, between 1990 to 1993, a survey of the intensive care units of 400 hospitals recorded an increase from 3.6% to 14.4% in ESBL producing

strains of*Klebsiella*. In 1994, the CDC reported that 8% of *Klebsiella spp* from a few large centers produced ESBLs. In Europe, as of 1995, ESBLs occurred in 20%-25% of*Klebsiella ssp* from patients in ICUs, although they were found in patients up to 30%-40% frequency in France.

Known risk factors for colonization and/or infection with organisms harboring ESBLs include admission to an intensive care unit, recent surgery, instrumentation, prolonged hospital stay and antibiotic exposure, especially to extended-spectrum beta-lactam antibiotics. Use of extended-spectrum antibiotics exerts a selective pressure for emergence of ESBL producing strains. The resistance plasmids can then be transferred to other bacteria, not necessarily of the same species, conferring resistance to them.

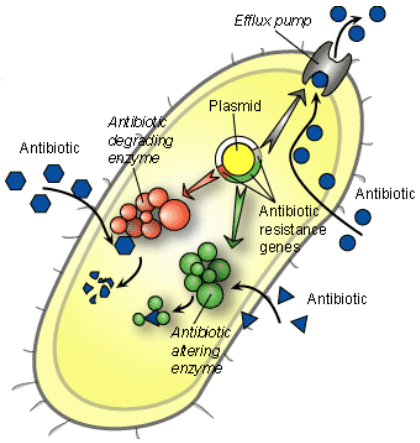
The lower GI tract of colonized patients is the main reservoir of these organisms. Gastrointestinal carriage can persist for months. In some cities in the United States, nursing homes may be an important reservoir of ESBL producing strains. Nursing home patients are more likely to be treated empirically with antibiotics, and thus on admission to a hospital to be more likely to possess an ESBL producing strain. Patient to patient transmission of ESBL producing organisms occurs via the hands of hospital staff. It is known that ESBL producing strains can survive in the hospital environment.

Nosocomial infections in patients occur through the administration of extended spectrum beta-lactam antibiotics or via transmission from other patients via health care workers, who become colonized with resistant strains via exposure to patients or other health care workers. Spread of ESBL producing strains can be minimized by good infection control practices, especially by good hand washing technique.

Bacterial mechanisms of antibiotic resistance

Several mechanisms have evolved in bacteria which confer them with antibiotic resistance. These mechanisms can either chemically modify the antibiotic, render it inactive through physical removal from the cell, or modify target site so that it is not recognized by the antibiotic.

The most common mode is enzymatic inactivation of the antibiotic. An existing cellular enzyme is modified to react with the antibiotic in such a way that it no longer affects the microorganism. An alternative strategy utilized by many bacteria is the alteration of the antibiotic target site. These and other mechanisms are shown in the the figure and accompanying table below.



Mechanisms of antibiotic resistance in bacteria

Antibiotic	Method of resistance
Chloramphenicol	reduced uptake into cell
Tetracycline	active efflux from the cell
β-lactams, Erythromycin, Lincomycin	eliminates or reduces binding of antibiotic to cell target
β-lactams, Aminoglycosides, Chloramphenicol	enzymatic cleavage or modification to inactivate antibiotic molecule
Sulfonamides, Trimethoprim	metabolic bypass of inhibited reaction
Sulfonamides, Trimethoprim	overproduction of antibiotic target (titration)

The acquisition and spread of antibiotic resistance in bacteria

The development of resistance is inevitable following the introduction of a new antibiotic. Initial rates of resistance to new drugs are normally on the order of 1%. However, modern uses of antibiotics have caused a huge increase in the number of resistant bacteria. In fact, within 8-12 years after wide-spread use, strains resistant to multiple drugs become widespread. Multiple drug resistant strains of some bacteria have reached the proportion that virtually no antibiotics are available for treatment.

Antibiotic resistance in bacteria may be an inherent trait of the organism (e.g. a particular type of cell wall structure) that renders it **naturally resistant**, or it may be **acquired** by means of mutation in its own DNA or

acquisition of resistance-conferring DNA from another source.

Inherent (natural) resistance. Bacteria may be inherently resistant to an antibiotic. For example, an organism lacks a transport system for an antibiotic; or an organism lacks the target of the antibiotic molecule; or, as in the case of Gram-negative bacteria, the cell wall is covered with an outer membrane that establishes a permeability barrier against the antibiotic.

Acquired resistance. Several mechanisms are developed by bacteria in order to acquire resistance to antibiotics. All require either the modification of existing genetic material or the acquisition of new genetic material from another source.

Vertical gene transfer

The spontaneous mutation frequency for antibiotic resistance is on the order of about of about 10^{-8}- 10^{-9}. This means that one in every every 10^{8}- 10^{9} bacteria in an infection will develop resistance through the process of mutation. In *E. coli*, it has been estimated that streptomycin resistance is acquired at a rate of approximately 10^{-9} when exposed to high concentrations of streptomycin. Although mutation is a very rare event, the very fast growth rate of bacteria and the absolute number of cells attained means that it doesn't take long before resistance is developed in a population.

Once the resistance genes have developed, they are transferred directly to all the bacteria's progeny during DNA replication. This is known as **vertical gene transfer** or **vertical evolution**. The process is strictly a matter of Darwinian evolution driven by principles of natural selection: a spontaneous mutation in the bacterial chromosome imparts resistance to a member of the bacterial population. In the selective environment of the antibiotic, the wild type (non mutants) are killed and the resistant mutant is allowed to grow and flourish

Horizontal gene transfer

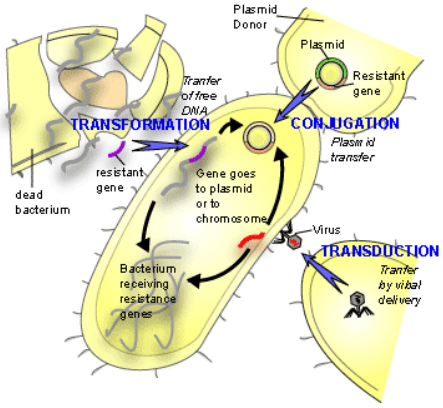
Another mechanism beyond spontaneous mutation is responsible for the acquisition of antibiotic resistance. Lateral or **horizontal gene transfer** (HGT) is a process whereby genetic material contained in small packets of DNA can be transferred between individual bacteria of the same species or even between different species.

There are at least three possible mechanisms of HGT, equivalent to the three processes of genetic exchange in bacteria. These are transduction, transformation or conjugation.

Conjugation occurs when there is direct cell-cell contact between two bacteria (which need not be closely related) and transfer of small pieces of DNA called plasmids takes place. This is thought to be the main mechanism of HGT.

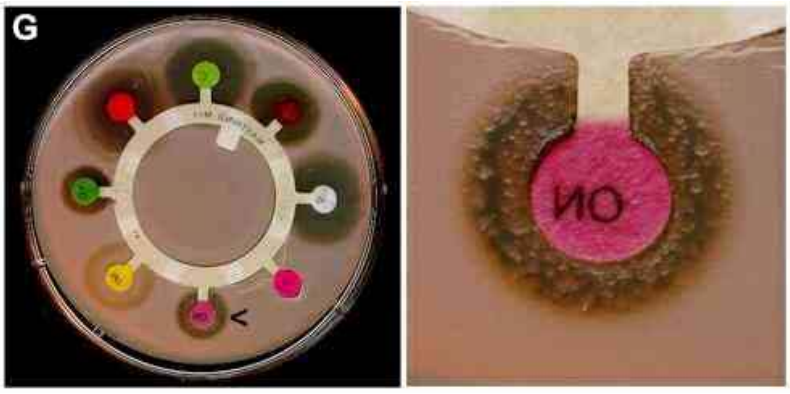
Transformation is a process where parts of DNA are taken up by the bacteria from the external environment. This DNA is normally present in the external environment due to the death and lysis of another bacterium.

Transduction occurs when bacteria-specific viruses (bacteriophages) transfer DNA between two closely related bacteria.



Mechanisms of horizontal gene transfer (HGT) in bacteria

The combined effects of fast growth rates to large densities of cells, genetic processes of mutation and selection, and the ability to exchange genes, account for the extraordinary rates of adaptation and evolution that can be observed in the bacteria. For these reasons bacterial adaptation (resistance) to the antibiotic environment seems to take place very rapidly in evolutionary time. Bacteria evolve fast!



Tests for sensitivity and resistance to antibiotics. (Left) The size of the zones of inhibition of microbial growth surrounding the antibiotic disks on the plate are an indication of microbial susceptibility to the antibiotic. (Right) By the use of these disks it is also possible to detect the occurrence of individual mutants within the culture that have developed antibiotic resistance. This image shows a close-up of the novobiocin disk (marked by an arrow

on the whole plate) near which individual mutant cells in the bacterial population that were resistant to the antibiotic and have given rise to small colonies within the zone of inhibition.

Societal, medical and agricultural practices that lead to antibiotic resistance

In the face of a microbe's inherent ability to develop antibiotic resistance, many societal. medical and agricultural practices contribute to this process, foremost of which are discussed below.

Antibiotics in food and water

Prescription drugs are not the only source of antibiotics in the environment. In the United States, antibiotics can be found in beef cattle, pigs and poultry. **The same antibiotics then find their way into municipal water systems when the runoff from housing facilities and feedlots contaminates streams and groundwater**. So it's a double hit: we get antibiotics in our food and drinking water, and we meanwhile promote bacterial resistance. Routine feeding of antibiotics to animals is banned in the European Union and many other industrialized countries. Maybe they know something we don't.

Indiscriminate use of antibiotics in agriculture and veterinary practice

The non-therapeutic use of antibiotics in livestock production makes up at least 60 percent of the total antimicrobial production in the United States. Irresponsible use of antibiotics in farm animals can lead to the development of resistance in bacteria associated with the animal or with people who eat the animal. Such resistance can then be passed on to human pathogens by mechanisms of HGT.

Of major concern is the use of antibiotics as feed additives given to farm animals to promote animal growth and to prevent infections (rather than cure infections). The use of an antibiotic in this way contributes to the emergence of antibiotic-resistant pathogens and reduces the effectiveness of the antibiotic to combat human infections.

Antibiotic resistance in genetically modified crops

Antibiotic-resistance genes are used as "markers" in genetically modified crops. The genes are inserted into the plant in early stages of development to in order to detect specific genes of interest . e.g. herbicide-resistant genes or insecticidal toxin genes. The antibiotic-resistance genes have no further role to play, but they are not removed from the final product. This practice has met with criticism because of the potential that the antibiotic-resistance genes could be acquired by microbes in the environment. In some cases these marker genes confer resistance to front-line antibiotics such as the beta-lactams and aminoglycosides.

Inappropriate use of antibiotics in the medical environment

One problem is the casual use of antibiotics in medical situations where they are of no value. This is the fault of

both health care workers and patients. Prescribers sometimes thoughtlessly prescribe 'informed' demanding patients with antibiotics. This leads to use of antibiotics in circumstances where they are of not needed, e.g. viral upper respiratory infections such as cold and flu, except when there is serious threat of secondary bacterial infection. Another problem is patient failure to adhere to regimens for prescribed antibiotics.

Patients and doctors need to realize their responsibility when they begin an antibiotic regimen to combat an infectious disease. There are several measures that should be considered.

ï¿½ Patients should not take antibiotics for which there is no medical value (corollary: doctors should not prescribe antibiotics for which there is no medical value).

ï¿½ Patients should adhere to appropriate prescribing guidelines and take antibiotics until they have finished.

ï¿½ Patients should be give combinations of antibiotics, when necessary, to minimize the development of resistance to a single antibiotic (as in the case of TB).

ï¿½ Patients need to be given another antibiotic or combination of antibiotics if the first is not working.

Combating antibiotic resistance

The following are recommendations to combat the development of antibiotic resistance in bacteria and other microorganisms.

Search for new antibiotics. To combat the occurrence of resistant bacteria, biotechnology and pharmaceutical companies must constantly research, develop and test new antimicrobials in order to maintain a pool of effective drugs on the market.

Stop the use of antibiotics as growth-promoting substances in farm animals. Of major concern is the use of antibiotics as feed additives given to farm animals to promote animal growth and to prevent infections rather than cure infections. The use of such antibiotics contributes to the emergence of antibiotic-resistant bacteria that threaten human health and decreases the effectiveness of the same antibiotics used to combat human infections.

Use the right antibiotic in an infectious situation as determined by antibiotic sensitivity testing, when possible.

Stop unnecessary antibiotic prescriptions. Unnecessary antibiotic prescriptions have been identified as causes for an enhanced rate of resistance development. Unnecessary prescriptions of antibiotics are made when

antibiotics are prescribed for viral infections (antibiotics have no effect on viruses). This gives the opportunity for indigenous bacteria (normal flora) to acquire resistance that can be passed on to pathogens.

Finish antibiotic prescriptions. Unfinished antibiotic prescriptions may leave some bacteria alive or may expose them to sub-inhibitory concentrations of antibiotics for a prolonged period of time. *Mycobacterium tuberculosis* is a slow growing bacteria which infects the lung and causes tuberculosis. This disease kills more adults than any other infectious disease. Due to the slow growing nature of the infection, treatment programs last for months or even years. This has led to many cases on unfinished prescriptions and 5% of strains now observed are completely resistant to all known treatments and hence incurable.

Several other possible solutions have been proposed or implemented to combat antibiotic resistance.

In the pharmaceutical industry, past and current strategies to combat resistance have not been effective. Pharmaceutical companies are seeking new, less costly strategies to develop antibiotics.

A decrease in the number of prescriptions for antibiotics, especially in small children, is occurring.

Several countries such as the UK have regulations concerning the use of antibiotics in animal feed.

Large scale public health education efforts are underway to stress the importance of finishing prescriptions. Indeed, in many places, failure to finish tuberculosis prescriptions can result in jail time.

Summary

The discovery of antibiotics was a leap in modern medicine. They have been able to stop the growth or kill many different kinds of microorganisms. However, bacteria have proven to be much more innovative and adaptive than we imagined and have developed resistance to antibiotics at an ever increasing pace. Bad practices and mismanagement have only exacerbated the situation. We could soon return to a state of medical health that was as dire as that which occurred prior to antibiotic use. However, with more research, education of the public, and well thought out regulations, the problems
can be solved. Several strategies are currently used to find new antibacterial compounds and new strategies are in development and trial.

Not only is there a problem in finding new antibiotics to fight old diseases (because resistant strains of bacteria have emerged), there is a parallel problem to find new antibiotics to fight new diseases. In the past three decades, many "new" bacterial diseases have been discovered (*E. coli* O157:H7 gastric ulcers, Lyme disease, toxic shock

syndrome, "skin-eating" streptococci). Already broad patterns of resistance exist in these pathogens, and it seems likely that we will soon need new antibiotics to replace the handful that are effective now against these bacteria, especially as resistance begins to emerge among them in the selective environment antibiotic chemotherapy.

It is said that the discovery and use of antibiotics and immunization procedures against infectious disease are two developments in the field of microbiology that have contributed about twenty years to the average life span of humans in developed countries where these practices are employed. While the greater part of this span in time is probably due to vaccination, most of us are either still alive or have family members or friends who are still alive because an antibiotic conquered an infection that otherwise would have killed them. If we want to retain this medical luxury in our society we must be vigilant and proactive We must fully understand how and why antimicrobial agents work, and why they don't work, and realize that we must maintain a stride ahead of microbial pathogens that can only be contained by antibiotic chemotherapy.

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FIVE DANGEROUS MYTHS ABOUT ANTIBIOTICS

Antibiotics Experts

http://www.antibioticsexpert.com/five-dangerous-myths-about-antibiotics.html

After the anthrax attacks of 2001, thousands of Americans took the antibiotic Cipro (ciprofloxacin) prophylactically in fear that they had been exposed to the deadly anthrax bacterium.

Unfortunately, while fewer than one in 5,000 had actually been exposed to the disease, about one in five users of the antibiotic suffered serious side effects, including hives, swelling of the throat, and difficulty breathing.

Even though many people think that antibiotics are harmless, these potent infection fighters actually can endanger your health and the health of your family if they are not used properly. Here are the top five myths about antibiotics and why not having the facts can cause you harm.

Myth number 1: It’s a good idea to stock up on antibiotics in case there is a shortage when you get sick.

The number one fear of survivals is an outbreak of bird flu. Although there undoubtedly would be uses for antibiotics during a bird flu epidemic, antibiotics would do nothing to treat that particular viral infection. Moreover, storing antibiotics past their expiration date causes unpredictable variations in their potency. An antibiotic like

Cipro you have had sitting on a shelf at room temperature for 2 or 3 years may be less potent or so much more potent that it costs deadly drug interactions. Antibiotics that are used after their expiration date may even cause kidney or liver damage.

Myth number 2. Antibiotics will help you get over colds or flu.

The only microorganisms antibiotics kill are bacteria (and not every antibiotic is effective against every strain of bacteria). Colds and flu are caused by viruses that are unaffected by antibiotics. Doctors used to accede to patient requests and prescribe antibiotics anyway, but nowadays the problem of antibiotic resistance is so great most doctors will refuse to prescribe them when patients present viral symptoms.

Myth number 3. Antibiotic resistance is itself a myth.

Unfortunately, the ability of bacteria to gain resistance to antibiotics is very real. Especially when someone takes just part of their prescribed pills, a few bacteria will survive treatment. These virulent bacteria can then exchange their genetic material with weaker bacteria, creating a superstrain that no antibiotic can handle. That's what has happened with MRSA, methicillin-resistant Staphylococcus aureus, the devastating skin disease that can be spread in locker rooms, hot tubs, hospitals, and jails.

Myth number 4. It's OK to take antibiotics even if you aren't really sick.

Any time you take any drug you risk side effects. If you are taking an antibiotic prescribed for someone else that's been on the shelf for an extended period of time, you are risking serious side effects. And if you try to use antibiotics when are not infected with disease-causing bacteria, you (1) kill the symbiotic bacteria that digest fiber and manufacture B vitamins and vitamin K in your colon and (2) potentially create a strain of bacteria that previously was benign.

Myth number 5. It's OK to stop antibiotics as soon as you feel better.

If you stop taking antibiotics before you have finished your prescription, you may feel OK for the short term but risk a much more serious infection in the long term. If you take just enough antibiotic to kill 99 per cent of your infection, you will likely have a 99 per cent reduction in symptoms. The problem is, that last 1 per cent of bacteria will have survived the first few days of treatment, and can pass on its offspring so that they too can survive the

first few days of treatment. Next time, you or someone you infect will not get relief as quickly from antibiotic therapy, and maybe not at all.

It is not easy for scientists to create newer, stronger antibiotics. Only by using antibiotics carefully and completely can we keep them effective against new infections in the future.