Drug-resistant germs: a global crisis

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In April this year, the *Boston Globe* reported the death of a 70-year-old man in Port Chester, New York after he became infected with the bacteria Staphylococcus aureus. The potent antibiotic vancomycin, considered the most powerful and reliable drug available, proved unable to counter the bacteria.

He was the first patient to die of the infection. In three previous cases in which vancomycin-resistant strains were identified, the microbe remained susceptible to other drugs. But in the fourth instance, the patient was dead 12 hours after treatment began.

Dr Stuart Levy, president of the American Society for Microbiology and president of the Alliance for the Prudent Use of Antibiotics, warned that the death highlighted 'concerns raised by many that a high level, fully vancomycin-resistant organism will emerge before the end of this century.'

Staphylococcus aureus is a major cause of hospital-acquired infections. Strains already exist around the world which are resistant to all antibiotics except vancomycin. Now the bacteria have moved one step closer to becoming unstoppable killers, impervious to the use of all known drugs.

The microbe is found in the nose and throat and on the hair and skin of 50 percent of healthy individuals. It can also be found in air, dust, sewage and surfaces of food processing equipment. If allowed to grow it produces a toxin which is not destroyed by cooking or canning processes and which causes nausea, vomiting, abdominal cramping, diarrhea and fever.

Vancomycin-resistant S. aureus is only part of a broader health crisis. At least three other bacterial species, all potentially life threatening, are now resistant to more than 100 different drugs:

• Mycobacterium tuberculosis is one of the major infectious human diseases. Commonly transmitted by coughing, the bacteria enter via the mouth, are inhaled into the lungs and set up a primary tubercle. The tubercle can spread to the lymph nodes and then into the bloodstream, setting up millions of tiny tubercles throughout the body. The incidence of tuberculosis or TB, always prevalent in underdeveloped countries, is on the rise again in industrialised nations. Multidrug-resistant tuberculosis was first reported in New York City and Florida.

• Enterococcus faecalis is associated with intra-abdominal and pelvic infections and can cause endocarditis, an inflammation of the lining of the heart cavity.

• Pseudomonas aeruginosa causes infections of the respiratory tract.

What is an antibiotic?

An antibiotic is a substance produced by or derived from a microorganism that inhibits or destroys bacterial growth, giving a person's immune system a chance to overcome the bacteria that remain. The drugs work by entering the microbes and interfering with the production of new bacterial cells.

Antibiotic is derived from the word antibiosis, which was first used in the 1880s to describe the destruction of one living thing by another. Antibiosis exists throughout the world of living things--bacteria, for example, attack other organisms in order to obtain nourishment and to reproduce, as do moulds, which exist as parasites on other species.

Attempts to use substances derived from one organism to inhibit or kill others began at least 2,500 years ago. The Chinese became aware of the curative properties of the mouldy curd of soybeans and used this substance to treat boils, carbuncles, and similar infections.

The first suggestion that the antagonism between two different bacterial species might be important in treating disease was made by Louis Pasteur and Jules-Francois Jourbert in 1877. They discovered that the bacteria responsible for anthrax grew rapidly if inoculated into urine free from micro-organisms, but died if common-air bacteria were present.

But it was not until 1928 that the antibiotic era began with the discovery of penicillin by Alexander Fleming. Fleming observed that a growth culture of the bacterium Staphylococcus aureus had disappeared in an area in which a green mould was growing. As the mould producing organism was a species of penicillium, Fleming named the derived drug penicillin.

Initial attempts to treat human infections with penicillin were largely unsuccessful as the substance was unstable. By 1941 the limitations had been overcome and the drug was used to treat serious infections. The results were dramatic. Patients who received penicillin made rapid and complete recoveries.

Since 1948 many antibiotics have been discovered that inhibit or kill bacteria, opening up a period sometimes referred to as the golden age of chemotherapy. With a few exceptions, antibiotics are the only drugs that can cure diseases by eliminating the immediate cause--micro-organisms. Antibiotics have saved countless lives and dramatically reduced the duration of diseases.

In the 1930s, the death rate for pneumonia patients ranged from 20 percent to 85 percent in the United States, but by the 1960s had fallen to about 5 percent. Fatalities from epidemic spinal meningitis, which once killed 20 percent to 90 percent of untreated victims, have been reduced to around 2 percent.

The statistics for typhoid fever, syphilis, gonorrhea and many other communicable diseases are similar. Antibiotics have also proven useful in preventing some infectious diseases, such as rheumatic fever, in susceptible people.

Drug-resistant strains

By 1977 pharmaceutical manufacturers began to think infectious diseases were conquered and cut back severely on searching for new antibiotics. If a drug failed, another one would be used and usually it worked. But over the last 20 years, this false optimism has been undermined by the emergence of multi-drug resistant germs.

How microbes become drug-resistant or insensitive to an antibiotic depends upon two factors--the prevalence of resistance genes in the bacteria and the extent of antibiotic use.

Resistance genes in bacteria combat the affects of antibiotics in a variety of complex ways. Some produce enzymes which degrade antibiotics by chemically modifying them. Others alter or replace molecules on the bacteria which the antibiotic uses to bind to its target. Still others manufacture 'pumps' to export antibiotics before they find their targets.

Bacteria can acquire resistance genes by different means. The gene can occur through mutations which are then passed on to the next generations. Or bacteria can acquire resistance genes directly from other bacterial cells in their vicinity.

Antibiotics promote the survival and propagation of resistant strains. An antibiotic will kill off highly susceptible cells. But other cells may survive if they have some resistance genes or begin to acquire them from other bacteria. As a result, cells with drug-resistant genes go on to reproduce.

The likelihood of drug-resistant strains emerging is particularly enhanced if the antibiotic dose is too low or if the course of treatment is too short to overwhelm the bacteria which are causing the disease.

Another process also takes place. Antibiotics not only attack disease-causing bacteria but impact on benign bacteria which are innocent bystanders. The drugs encourage the growth of drug-resistant bystander bacteria, increasing the reservoir of resistance traits which may then be passed on to more dangerous species.

Enterococcus faecalis was once a benign intestinal bacteria. But the widespread use of the drug Cephalosporin, to which E. faecalis had a natural resistance, has led to its widespread proliferation. In addition, the bacteria has developed a reservoir of vancomycin-resistance traits posing the danger that these may be passed on to multidrug-resistant bacteria such as S. aureus, making them incurable.

The formerly innocuous microbes Acinetobacter and Xanthomonas, virtually unheard of five years ago, have developed multidrug-resistance through the bystander effect and are causing fatal blood-borne infections in hospitalised patients.

The spread of drug-resistant strains

Antibiotic resistance that emerges in one place can often spread rapidly and over great distances as the bacteria spread to the surroundings and to new hosts. Technological and economic changes have accelerated the process. International travel and the increasingly global character of food handling, processing and sales have led to the spread of HIV/AIDS, tuberculosis, cholera and malaria, as well as drug-resistant bacteria.

The dangers of a global epidemic of drug-resistant diseases are increased by the growth of poverty, overcrowding, the lack of adequate sanitation and the deterioration of public health systems worldwide.

Health officials internationally point to over-prescription of antibiotics as the main cause of drug-resistant germs. While there is evidence to show that over-prescription, and in some instances the incorrect prescription of antibiotics, has played a major role in the development of drug-resistant germs, the question is why.

One answer lies in the fact that 40 years ago medical textbooks advised physicians to treat viral diseases with antibiotics in order to prevent secondary bacterial infections. A virus is not a bacterium nor an independently-living organism. Antibiotics do not harm or kill viruses. That is why treatment for influenza, a viral infection, is aimed at easing the symptoms rather than to killing the 'flu' virus.

Patient pressure on doctors has been identified as a significant factor in the overprescription of antibiotics. Research has shown that in the United States alone, over one third of all prescriptions are unnecessary. But this 'patient pressure' for some kind of relief from illnesses like the 'flu' is itself bound up with social questions--the growing pressures to go to work rather than take the needed time to recuperate at home.

But pressures are also exerted on doctors by the major drug companies. Billions of dollars are made through the worldwide sale of antibiotics which are pushed through extensive promotional and advertising campaigns. In many underdeveloped countries a doctor's prescription is not required and antibiotics can be bought over the counter at any pharmacy.

If official attitudes are changing to antibiotic use, it is not just because of concerns over the emergence of drug-resistant strains. Governments everywhere are cutting funding for public health care and hospitals. Antibiotics have been targeted for cutbacks in particular because they represent a high single-cost item.

Antibiotics in agriculture

The overuse of antibiotics is not limited to medicine. Scientists have long suspected that the use of drugs in agriculture has contributed to the emergence of drug-resistant bacteria. Now there is strong evidence.

Since antibiotics first became available their use has soared. In the United States alone, annual production has risen from nearly a million kilograms in 1954 to about 25 million kilograms today. Only about half is used by human beings.

The same drugs prescribed for humans are widely used in animal husbandry and agriculture. More than 40 percent of the antibiotics manufactured in the US are given to animals, not in the main to fight infections but to promote growth. Animals are given low doses of the drugs over weeks or months in their feed--a perfect recipe for developing resistant bacteria.

Treating animals is also a means of reducing feed costs. Antibiotics, by killing bacteria in the stomach of animals, slows-down the digestive processes, thereby reducing the amount of food intake an animal requires.

A salmonella strain impervious to five antibiotics, known as DT104, is rampant in Britain. In the United States scientists say the same strain has sickened thousands of Americans and nearly killed a Vermont dairy farmer. The US Centre for Disease Control and Prevention (CDC) estimates that DT104 infects between 68,000 and 340,000 Americans annually.

The drug-resistant strain has developed as a result of the use of fluoroquinolones, powerful antibiotics that had been reserved for severely ill people. But in 1995, the US Federal Department of Agriculture (FDA) approved two types of fluoroquinolones for use in poultry. The drugs are put into chicks' drinking water to prevent a flock-destroying disease.

Exposure to the fluoroquinolones caused the bacteria, campylobacter, the leading human food poisoner, to mutate rapidly. Of 76 chicken products tested in Minneapolis-St Paul grocery stores last year, 79 percent were contaminated with campylobacter. In 20 percent of the samples, the bacteria were fluoroquinolone-resistant.

The drug-resistant strain was found in 13 percent of human cases involving campylobacter tested in the US last year. According to CDC researcher Dr Frederick Angulo, such cases were unknown prior to 1995.

Avoparcin, an antibiotic closely related to vancomycin, was banned in Europe last year, after being used to increase animal growth. Since the ban, preliminary evidence suggest vancomycin-resistant germs in poultry have reduced.

Despite the availability of these research results, the drug company Bayer has asked the FDA to allow the expanded use of fluoroquinolones into cattle.

Scientists are also concerned about the use of antibiotic sprays in agriculture such as the application of aerosols to fruit trees as a means of controlling or preventing bacterial infections. While high concentrations kill all the bacteria on the trees at the time of spraying, lingering residues can encourage the growth of resistant bacteria that later colonise the fruit during processing and shipping. Residue from the aerosols can be carried considerable distances in a much-diluted form. While it is too weak to kill off infections, it is still capable of killing off sensitive bacteria and in this way strengthening resistant strains.

The level of resistant bacteria that people acquire from food is significant. Research done by the National Institute for Agricultural Research in Toulouse, France showed that when human volunteers went on a diet consisting only of bacteria-free foods, the number of resistant bacteria in their faeces decreased 1000-fold. Scientists suspect that we deliver resistant strains of microbes to our intestinal tract whenever we eat raw or undercooked items. Most of these bacteria are not harmful, but danger arises if food is contaminated by a disease-causing strains.

Reversing bacterial resistance to antibiotics requires further knowledge and the development of other medical strategies. Treatments that enhance a person's own immune system to combat bacterial infection without the need of antibiotics are yet to be fully investigated.

In the past, bacteria were regarded as bad and to be wiped out. Now, scientists recognise that bacteria are a natural and necessary part of life. Some in fact protect us from disease. Only those bacteria that give rise to disease should be eliminated. Curing bacterial disease has to be combined with preserving microbial communities so that bacteria susceptible to antibiotics will always be present to outcompete resistant strains.

The overuse of antibiotics both in farming and in the general population is bound up with serious social and political questions. It is driven by the profit requirements of agribusinesses and drug companies. As in other spheres of life, a fundamental solution requires the total reorganisation of society to free science, farming and health care from the dictates of corporate profit.

See Also:

Reports document worldwide epidemic
The worst year in history for tuberculosis
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