SOME 68 years ago, in March 1942 to be precise, a 33-year-old woman lay dying of streptococcal sepsis (an infection caused by the bacteria of the genus *Streptococcus*) in a Connecticut hospital in the United States of America. Despite the best efforts of contemporary medical science, the doctors could not get rid of her bloodstream infection. Somehow, they managed to obtain a small amount of a newly discovered substance called penicillin – discovered by Alexander Fleming in 1928 but not yet available off the shelf. They cautiously injected it into her. After repeated doses, her bloodstream was cleared of streptococci, and she recovered fully. The woman went on to live to the age of 91!

Sixty-six years after her startling recovery, in 2008, a report described a 70-year-old man in San Francisco, USA, with endocarditis (inflammation of endocardium – the lining membrane of the heart). This condition was caused by the *Enterococcus faecium* bacteria that were resistant to the antibiotic vancomycin, a drug of choice of the day. Despite administration for many days of the best antibiotics available for combating these vancomycin-resistant *Enterococcus faecium* (VRE) bacteria, physicians were unable to sterilise the patient’s blood, and he died with the bacteria still present in his blood.

In a recent issue, the British medical journal *The Lancet Infectious Diseases* (published online on 11 August 2010), published a paper revealing the rapid spread of drug-resistant bacteria. The authors reported that they tracked down a ‘superbug’ to Indian hospitals, that has already spread to Pakistan, Bangladesh, and the UK, and is resistant to almost all antibiotics available in the market today. This superbug infects patients and causes multiple organ failure. We may note that ever since the paper was published, it has generated heated debates around the world on the prospects of the superbug spreading across the world, and in particular, on the booming Indian medical tourism industry. The authors also posed a question - “Is this the end of antibiotics?” Does this sound like an exaggeration? Perhaps not!

Today, for patients infected with multidrug-resistant bacteria, there are no magic bullets available. We have come almost a full circle and arrived at a point as frightening as the pre-antibiotic era. Today, it is difficult, almost impossible, to think of undertaking surgeries, transplantations, cancer chemotherapy, care of HIV-infected or the critically ill, without effective antimicrobial agents. However, a few microbes (bacteria, viruses, and some parasites) have adapted to a point where they pose serious clinical challenges for humans. And, for sure, bacteria are the champions of evolution! In just a couple of generations, what once appeared to be miracle drugs have been reduced to ineffectiveness by the very bacteria they were designed to knock out! How did it all happen?

**A World Without Antibiotics?**

VINAY B. KAMBLE

There have been heated debates ever since *The Lancet* published an article on the superbug NDM-1. But the challenge posed by antibiotic resistant strains of bacteria is real and cannot be brushed aside. Almost each one of us has used an antibiotic – for a bad cut, or to get over pneumonia, or some other type of infection. Antibiotics are chemicals, which when introduced into our body stop the growth of certain kinds of germs, called bacteria, and help our body fight disease. Indeed, human beings have been using antibiotics for over 3,000 years. The Chinese and the Egyptians stumbled upon some moulds that could be used as a cure to treat rashes and wounds. Sumerians used beer soup mixed with snakeskins and turtle shells. Indians and Greeks used many herbs to heal several ailments. All of these natural treatments contained some sort of antibiotic. With passage of time, people began to gain some insight into diseases. In the 1860s, Louis Pasteur (1822-1895) showed that many diseases were caused by bacteria. He later recognised that one type of bacteria could be used to kill another type of bacteria.

**Antibiotics – 3,000 years old**

In 1929, Sir Alexander Fleming (1881-1955), a Scottish bacteriologist, made the real breakthrough in antibiotics. He went on a vacation and left a petri dish of staphylococci bacteria uncovered. When he returned, he noticed that there was mould growing on it. Upon further examination, he saw that the area around the mould had no bacteria growing, thanks to a chemical produced by the mould. The name of the mould was penicillium, and hence...
the chemical produced by the mould was named penicillin - the first ever substance recognised as an antibiotic. Penicillin worked against pneumonia, scarlet fever, and several other diseases; however, it had no effect on germs that caused typhoid, influenza, and many other diseases. As a result, scientists had to continue their search for other antibiotics. Mass production of penicillin, however, began only in the mid-1940s.

After penicillin came the discovery of the sulpha drugs. They came from Prontosil, a substance used as a dye. When introduced into the body, Prontosil changes into an active germ-killing drug called sulphonamide. This drug could cure pneumonia, scarlet fever, and blood poisoning. In the late 1940s through the early 1950’s, streptomycin (used in treatment of tuberculosis, typhoid fever and other infections), chloramphenicol (used in the treatment of typhoid fever, some form of meningitis and as drops or ointments for skin, eye, or ear infections), and tetracycline (prescribed to treat urinary infections, pneumonia, diseases such as typhus, sexually transmitted infections and conjunctivitis caused by the “chlamydia” bacteria) were discovered and introduced as antibiotics.

However, it is interesting to note that almost immediately after penicillin was introduced, resistance in certain strains of staphylococci was noticed. By 1950’s it was apparent that tuberculosis bacterium was rapidly developing resistance to streptomycin, which had commonly been used to treat it. In 1953, during a Shigella outbreak in Japan, a certain strain of dysentery bacillus was found to be resistant to chloramphenicol, tetracycline, streptomycin, and the sulphonamides.

Bacteria and Antibiotics

When, one gets a cut or is injured, it results in breakage or opening of the skin barrier, through which some opportunistic pathogens gain entry into the body. If the person is healthy and has a strong immune system, it fights off the unwanted entry. However, if a person is weak or the pathogen is virulent, it results in development of a disease caused by bacteria. The bacteria that cause health problems in human beings are called human pathogenic bacteria. They can also gain entry into the body through food, water, air, saliva and other body fluids.

Billions of bacteria belonging to hundreds of different species - both identified and unidentified - inhabit the human body, forming an ecological community living in a state of equilibrium. Their number in our body is nearly 10 times higher than the number of cells in our body! Most of them are benign to the host and some even provide valuable services.
negative. A technique for preliminary identification of bacteria was developed by Hans Christian Joachim Gram (1853-1938), a Danish physician, in which a violet dye is applied, followed by a decolourising agent and then a red dye. The cell walls of bacteria that retain the first dye and appear violet are termed the Gram-positive bacteria, while those that lose it appear red and are termed Gram-negative bacteria.

Gram-positive bacteria are encased in a plasma membrane covered with a thick wall of peptidoglycan. Gram-negative bacteria are encased in a triple-layer, the outermost layer containing lipopolysaccharide. Because of their thick cell wall, Gram-positive bacteria were considered more difficult to treat than the Gram-negative ones, but this is no longer true. In fact, it is the Gram-negative bacteria that have now developed resistance to most potent antibiotics.

Bacteria could be rod-shaped (bacilli), spherical (cocci), or may even have curved walls (spirilla). They even may have a tendency to bunch like grapes as in the case of staphylococcus.

**Survival of the Fittest**

Bacteria do not have a membrane-bound nucleus, and their genetic material is typically a single circular chromosome located in the cytoplasm in an irregularly shaped body called the nucleoid. The nucleoid contains the chromosome DNA (deoxyribonucleic acid) with associated proteins and ribonucleic acid (RNA). It also contains plasmids, which are DNA molecules. Plasmids are separate from, and can replicate independently of, the chromosomal DNA. Further, like all living organisms, bacteria contain ribosomes for the production of proteins, though their structure is different from ribosomes found in other organisms.

The indiscriminate and improper use of antibiotics results in a survival-of-the-fittest selection process for bacteria, which can both inherit and acquire resistance to drugs, through mutation or by sharing DNA. This is just as in normal Darwinian evolution, but accelerated umpteen times by the division of millions of them. Further, this also holds true for other microbes (an umbrella term for microscopic organisms that include bacteria, viruses, fungi and parasites). An infection treated with the wrong drug or for too short a time results in most bacteria being killed while the resistant ones survive to multiply. Antibiotics are ineffective against viral infections; if used they promote the growth and spread of resistant microbes in patients, their families, and the community. The lack of effective monitoring and enforcement of controls on the sale and use of antibiotics is cited by the World Health Organization (WHO) as one of the main causes of growing resistance of the world’s microbes to antimicrobial drugs.

Bacteria and other microbes are transmitted readily from person to person and global travel has only contributed to the dissemination of novel pathogens, including drug-resistant strains. It is important to note that crowding also contributes to the dissemination of novel pathogens. Hospitals and nursing homes are particularly ideal environments for the exchange of microbes including drug-resistant strains. Cancer treatments and use of other immunosuppressives (drugs that reduce body’s normal...
deployed in the early 1940s. Resistance to antibiotics. Have become resistant to most antibiotics. Today, some low-grade hospital bugs were discovered. In the 1980s and 1990s, scientists could only manage to do prophetic!

Emergence of the Superbugs
As early as 1945, in an interview with The New York Times, Fleming warned that the misuse of penicillin could lead to selection of resistant forms of bacteria. Fleming had experimentally derived such strains by varying the dosage and conditions upon which he added the antibiotic to bacterial cultures. Fleming had warned that the drug carried a large potential for misuse, especially with patients taking it orally at home, and that inadequate treatments would likely lead to mutant forms. How his words have proved to be prophetic!

When first discovered, antibiotics were thought to be a miracle cure and they literally were. Infections that were fatal were reduced to mere inconveniences. In the early years, new antibiotics were developed faster than bacteria developed resistance to them. But the bugs caught up fast. In the 1950s and 1960s, many new classes of antibiotics were discovered. In the 1980s and 1990s, scientists could only manage to make improvements within classes. Today, some low-grade hospital bugs have become resistant to most antibiotics.

Penicillin and streptomycin were deployed in the early 1940s. Resistance to penicillin was observed in mid-1940s while resistance to streptomycin was observed in the late 1950s. Tetracycline was deployed in the late 1940s, but resistance to it was observed in mid-1950s. Erythromycin had a relatively long innings. Developed in the mid-1950s, resistance to it was observed in the late 1980s. Resistance to Meticillin, developed in late 1950s, was observed in the early 1960s. Resistance to Ampicillin, developed in the mid-1960s, was observed in the mid-1970s.

Hospitals are not the only breeding grounds for these “superbugs”, as they have come to be known. A marked rise in drug-resistant bugs has been observed in community homes and other places that are home to vulnerable groups of people. Worldwide, a new drug-resistant strain of tuberculosis is causing concern, particularly as the disease is enjoying resurgence. Even if resistance to some antibiotics does not prevent treatment because others are available, it still costs a large sum of money. Alternative drugs are more expensive and have greater side effects.

As of now, we continue to face growing resistance among Gram-positive and Gram-negative pathogens that cause infection in the hospital and in the community. It is reported that the pathogens such as Enterococcus faecium (Gram-positive), Staphylococcus aureus (Gram-positive), Klebsiella pneumoniae (Gram-negative), Acinetobacter baumannii (Gram-negative), Pseudomonas aeruginosa (Gram-negative), and Enterobacter species (Gram-negative) – the so-called ESKAPE pathogens – cause the majority of US hospital infections today and effectively “escape” the effects of antibacterial drugs.

Data show rapidly increasing rates of infection due to methicillin-resistant S. aureus (MRSA), vancomycin-resistant E. faecium (VRE), and fluoroquinolone-resistant P. aeruginosa. More people now die of MRSA infection in US hospitals than of HIV/AIDS and tuberculosis combined. Furthermore, pan-antibiotic-resistant (that is, resistant to all antibiotics) infections now occur frequently. Several highly resistant Gram-negative pathogens - namely Acinetobacter species, multidrug-resistant (MDR) P. aeruginosa, and carbapenem-resistant Klebsiella species and Escherichia coli — are emerging as significant pathogens in both the United States and other parts of the world.

Superbug NDM-1
Of late, in the Indian sub-continent, Gram-negative Enterobacteriaceae strains, resistant to the powerful antibiotic carbapenem, are becoming more widespread, especially in India and Pakistan. Incidentally, the antibiotic carbapenem is considered to be the last line of treatment for infections caused by Gram-negative bacteria. How does the resistance arise?

The resistance arises on account of a new gene that is responsible for production of the metallo-beta-lactamase enzyme that makes the antibiotic carbapenem ineffective. This drug-resistant bacterial gene, the so-called superbug, was named New Delhi Metallo-beta-lactamase-1 (NDM-1) in 2009 when it was first identified in a Swedish national admitted to a hospital in New Delhi.

The Lancet paper reported that 44 isolates with NDM-1 were identified in Chennai, 26 in Haryana, 37 in the UK, and 73 in other places in India and Pakistan. NDM-1 was mostly found among the bacterial species Escherichia coli and Klebsiella pneumoniae, which were highly resistant to all antibiotics except to tigecycline and colistin. K pneumoniae isolates from Haryana were clonal (structurally identical), but bacteria producing NDM-1 from the UK and Chennai were clonally diverse. The findings in Haryana are especially worrisome since the isolates were from community-acquired infections, suggesting that NDM-1 is widespread in the environment. It could hence lead to epidemics for which we hardly have any antibiotics!

The study further reported that the carbapenem-resistant strain was seen in 37 UK patients, who had undergone elective and cosmetic surgery in India and Pakistan. We may note that prior to this study, a study published in
March 2010 in the *Journal of Association of Physicians of India*, 22 cases of carbapenem-resistant NDM-1 were collected within a span of just three months from a Mumbai hospital. Most isolates carried the NDM-1 gene on plasmids (circular strand of DNA in the bacterium). The potential of NDM-1 to be a worldwide public health problem is great, and co-ordinated international surveillance is needed.

Resistance to extended-spectrum beta-lactamase (ESBL) drugs like third-generation cephalosporins is less than 15% in developed countries. While in India, it is between 60 and 70%. For treatment of ESBL infections, carbapenem is reserved antibiotic and the last line of treatment - is the drug of choice as it has the lowest resistance rates and the broadest action against Gram-negative infections. However, its indiscriminate use has played a major role in the development of the carbapenem-resistant gene, including the new NDM-1 strain.

NDM-1 was unknown until a few years ago, but has begun to show up in the last three years. NDM-1 is, in all probability, still a hospital-acquired infection. Drug-resistant NDM-1 strains are a cause of worry because very few drugs are available to treat Gram-negative infections. NDM-1 gene is carried in the plasmids of the Gram-negative bacteria and hence its prevalence could increase quite fast. These plasmids can move from one bacterium to another, and even to different species.

**Era of Antibiotics Coming to a Close?**

In many ways, this may be true. Since development of a new antibiotic requires huge investment and relatively long time period to develop and market, the pharmaceutical companies have not shown a great deal of enthusiasm for difficult antibiotic research since the 1990s. People take heart medicines for life, unlike the antibiotics that they may take for a week or so. And because resistance means the drugs become useless after a while, there is just not much money in it!

There are no antibiotics in the pipeline either that have activity against NDM-1 producing *enterobacteriaceae*. May be, there is a bleak window of 10 years, where we shall need to use the antibiotics we have very wisely, according to the lead author of the study published in *The Lancet*. This is with the assumption that drug companies can and will get moving on discovering new antibiotics to treat the new bacterial infections during this period.

What could we do to reverse the growth of the resistant bacteria, then? Here are a few things you could keep in mind:

- **Antibiotics should be used only when they are truly needed and that too only under the supervision of a physician.**
- **It is essential to complete the full course of antibiotic therapy to ensure that all the pathogenic bacteria are killed.**
- **Do not skip doses since this causes the level of antibiotic in the blood to drop, giving a chance to some bacteria to survive and develop resistance to this drug.**
- **Physicians should not prescribe antibiotics even when they are not required.**
- **Also do not “demand” antibiotics from physicians or purchase from the friendly pharmacist over the counter – without any prescription – even for colds and other viral infections against which antibiotics are ineffective.**
- **Consider seeking non-antibiotic therapies for minor ailments. Indeed, approximately one third to one half of all antibiotic prescriptions are not even needed.**
- **The amount of resistant bacteria people acquire from food is significant; hence it is advisable to wash raw fruits and vegetables thoroughly.**
- **Washing hands frequently with regular soap and warm water is the best way to avoid spreading harmful microbes.**

It has been a continuous war between man and microbes – both vying to outwit each other. But, eventually it is the microbe that seems to be gaining the upper hand – and for which we are largely responsible. There is need to formulate stricter national control policies, strict control on administration of drugs, antiseptic conditions in hospitals and clean environment. But, the most important is education of people, including practising physicians and medical students, to prevent rampant and indiscriminate use of antibiotics.

There is still a good chance of keeping the prevalence low, provided a two-pronged approach is adopted: instituting a national antibiotic policy that restricts the use of carbapenem and other higher-end antibiotics to hospital settings and only for patients with severe infections, and having a national registry of drug-resistant strains. May be, then there could be a hope and way out of this impasse.

Finally, one last comment. Ever since the publication of *The Lancet* paper, there have been heated debates the world over. In the developed countries, due to the challenges posed by the NDM-1 superbug, while in India because it could affect it’s booming medical tourism industry. But one must not lose the focus. The challenge posed by NDM-1 is very real and the efforts must begin in order that we do not lose the battle against bacteria, even if we don’t win it!

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