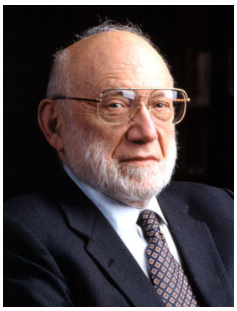
Have we created the ultimate antibiotic paradox?

Article written by: Derek Butler, Chairman, MRSA Action UK

In his book “Mirage of Health” the respected French microbiologist Rene Dubos wrote, “Since the days of the cave man, the earth has never been a garden of Eden but a valley of decision where resilience is essential to survival. To grow up in the midst of danger is the fate of the human race” in the face of microbes it has been one of survival and danger. There are many microbiologists who will say that the threat from microbes and viruses are over played and that the human race needs a doomsday scenario to replace the end of the cold war, so is this true you might ask.

Joshua Lederberg the American molecular biologist said that "The single biggest threat to man's continued dominance on the planet is the virus." Certainly we have seen what a Flu Pandemic can do in killing millions such as the one in 1918 and we have heard that bacteria and viruses are becoming stronger and fitter, with the ability to defeat whatever we challenge them with. If true, is it simply the bacteria mounting an immune response against the human race? Should we concern ourselves with this or just dismiss it as scare mongering?



We need to first look back at our association with microbes and viruses to understand these questions.

Bacteria have been around far longer than the human race, some 3 billion years, so they have a head start on mankind and have had plenty of time to learn to adapt to an ever changing planet. They survived the extinction of the dinosaurs some 65 million years ago.

Ever since man’s first tentative steps as a species we have been in constant conflict with bacteria and viruses. History is littered with examples of the suffering that bacteria and viruses can bring to the human race. Some of the earliest examples of this are written on Egyptian hieroglyphics showing a typical wasting of limbs that resulted from poliomyelitis. The most famous Egyptian Pharaoh, King Tutankhamen, is thought to have died from an infection (possibly staphylococcus aureus) from a broken leg as well as cerebral malaria.

hieroglyphics

The smallpox virus is a story of recent modern medicine success with its eradication worldwide. Although we are unsure where it originated, some think Africa spreading to India and China thousands of years ago, reaching Europe around Roman times. By the 18th century it was in every major city and country with the exception of Australia. Millions died from the disease.

Another scourge to mankind was Tuberculosis which was common in most European countries up to the 1960s. In fact from 1800 up to the 1960s Tuberculosis caused the deaths of over 700 million people and even as recently as the mid 20th century, it was still killing 3 million people a year. Today that figure is far less; however, resistant strains of this disease are appearing in western society.

Malaria, which has the distinction of having killed over half the people who have ever lived on earth, was once thought to have been brought under control. Yet today we are seeing strains that are becoming stronger and fitter against the treatments that we have developed against it.

Bubonic Plague or the Black Death has a high mortality rate of 1 to 15% if not diagnosed early. During medieval times the death rate was 1 in 3 of those who caught the disease.

The playing field was changed for bacterial microbes on the 28th September 1928, when Fleming discovered a mould in a dish. It was probably the greatest discovery in medical science, a discovery that would change the course of history.

The active ingredient that Fleming saw, and which he named penicillin, turned out to be an infection-fighting agent of the like the human race had never seen. When finally seen for what it was, believed to be the most efficacious life-saving drug in the world, penicillin, for the first time in mankind's history, gave it the leap ahead of bacterial infections that was needed.

Fleming's discovery gave birth to a huge pharmaceutical industry, churning out synthetic penicillin's that would conquer some of mankind's most ancient scourges, including the Black Death, gangrene, tuberculosis and staphylococci.

Fleming

However Fleming's discovery was two-fold, it enabled the development of newer and life saving treatments unthinkable at the time but common place today. Unknown to us at the time, it also opened Pandora's Box to the development of even stronger and fitter bacteria in the future. Bacteria had altered very little over millions of years before this date, however within a few years Fleming's discovery, penicillin, had started an evolution that helped to mutate bacteria into microbes far stronger and fitter than anything we had ever encountered.

Fleming warned in the New York Times (1945), that the misuse of penicillin could have the result that "microbes are educated to resist penicillin". The first occurring penicillin-resistant staphylococci were noted by Fleming in 1942. In 1947 the first superbug had appeared altered by the use of penicillin in the Hammersmith Hospital in London. The bacteria had produced penicillinase to counter the antibiotic penicillin and by the early 1950s, just over ten years after its introduction penicillin the wonder drug was rapidly losing its efficacy.

Two significant major developments followed in the late 1950s. The first was that scientists were now confident that they could counter resistance to penicillin and they produced a new wonder drug code named BRL 1241 which became known as methicillin, a new synthetic antibiotic. However Staphylococcus aureus quickly acquired a gene called mecA which quickly rendered the methicillin family of antibiotics useless within two years.

Consequently in 1963 the first outbreak of MRSA in a British hospital at Queen Mary's Hospital for Children at Carshalton in Surrey spread to 8 of the 48 wards, infecting 37 patients and killing one and was the first of many in the UK and across the world over the years to come.

The next significant development occurred in a hospital in Japan, alarming the whole scientific community – the birth of multiple drug resistant bacteria. A number of patients were suffering from Shigella dysentery. The bacteria causing this infection were resistant to tetracycline and the sulphonamides streptomycin and chloramphenicol. Multiple drug resistance was unknown prior to this. Now, it suddenly sent shock waves across the world.

Through spontaneous mutation, the genes of bacteria adapted, enabling them to survive in a hostile environment. It showed how changes in the environment could cause unseen changes in the world of bacteria. Through our ubiquitous use of antibiotics it had led to bacteria becoming even more adaptable. They developed new, improved survival mechanisms in the form of plasmids.

Plasmids are DNA molecules that carry genes that provide resistance to antibiotics and provide a mechanism for horizontal transfer. There seems to be no limit as to what bacteria will do in their response to antibiotics.

As if the production of plasmids was not enough, bacteria then developed transposons, producing spontaneous mutations. Transposons are the main method bacteria employ to survive in the presence of antibiotics. These are the mechanisms that have led to the epidemics of bacterial resistance that currently plague many modern hospitals.

Through our overuse of antibiotics, we had ensured the continuum of plasmids and transposons, their main function being to prevent bacteria from being killed by antibiotics. These plasmids and transposons were unknown until around the 1970s, when resistance was becoming a major problem. They started to ring the death knell for penicillin and were a warning of what was to come. A unique characteristic of plasmids is that they can be transferred from one bacterial cell to another and from one species of bacterium to another. This allows bacteria to become resistant to a drug very quickly.

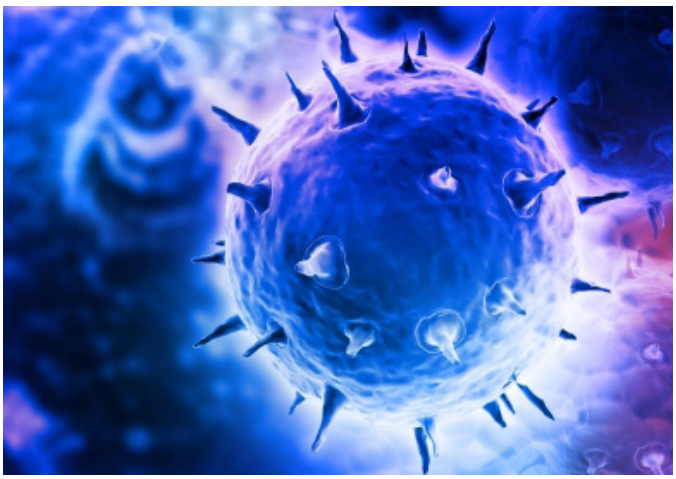
In the 1940s, 50s and 60s, antibiotics were developed at an ever accelerating rate, the confidence within the scientific community was such that it thought that bacterial infections were defeated and that the human race could keep ahead of the bacteria acquiring resistance to antibiotics. This period was commonly known throughout the scientific community as "continuous revolution".

The so called “continuous revolution” for antibiotics was over by the late 1970s as scientists found it harder to develop antibiotics against a growing army of ever stronger resistant bacteria. The bacteria were beginning to gain the upper hand and to add to this they were developing newer ways to counter what we were developing. They were becoming ever stronger and fitter by increasing the amount of DNA they were able to transfer to one another.

In 1999 a new development, a novel family of class B metallo-βeta-lactamases the VIM family, was discovered. This is an enzyme which attaches itself to a plasmid and was found in Pseudomonas aeruginosa, Acinetobactor, Escherichia coli and Klebsiella pneumonia.

In 2006 an outbreak involving a Pseudomonas aeruginosa strain that was resistant to all tested antimicrobials except polymyxin B occurred in a hospital in Houston, Texas. Previous studies on this strain showed that it possesses a novel mobile metallo-βeta-lactamase (MBL) gene, designated blaVIM-7, located on a plasmid.

In 2010 a new enzyme was discovered called New Delhi metallo-beta-lactamase (NDM-1).



NDM-1

This is a close genetic cousin of the enzyme blaVIM-7. The challenge in treating these bacteria is that both produce an enzyme that allows them to neutralise a group of antibiotics called carbapenems (one of the most powerful types of antibiotic available to doctors), which include penicillin and ampicillin.

These enzymes have the ability to make any bacteria resistant to all but a very few antibiotics. This development does make the bacteria stronger and fitter than ever against antibiotics.

MRSA, C.diff and E.coli are endemic in our hospitals. What would be the consequences if these enzymes could transfer resistance to each of these bacteria rendering our stock of antibiotics obsolete against them? What would be the consequences if the enzyme could transfer resistance from say HA-MRSA to CA-MRSA to produce a real superbug?

I believe we have now reached an impasse where the bacteria are so strong that the very antibiotics needed to counter this have to be even stronger which makes them dangerous to patients. Biotic means life.

The question is with the birth of antibiotics have we created such a paradox that we are heading toward a man-made plague of micro-organisms that will outwit us and become stronger than mankind?

Vaccines may be the only answer to this problem in the future and there is promising work being performed.

Charles Darwin wrote, “*It is not the strongest of species that survive, or the most intelligent, but the one most responsive to change*”.

By our actions, bacteria both old and modern, have become stronger and fitter and will become harder to control unless we take the initiative and become more responsive to change.

MRSA Action UK

For further information please contact:

Derek Butler
Chairman
MRSA Action UK

Tel: +44 (0) 7762 741114
www.mrsaactionuk.net