The Antibiotic Resistance are Fighting Bac - teria

In the dead of night, Ambrose sneaked out of the hospital and into a dark alleyway to join The Antibiotic Resistance – a group of bacteria determined to fight back against doctors and save their species from eradication. It was there that he became a member of the MRSA (methicillin resistant Staphylococcus aureus): an elite team equipped to survive extreme conditions and cause deadly diseases.

Antibiotics, the collective term for the medications used to treat bacterial infections, have saved millions of people, improved quality of life and progressed livestock farming. A world without antibiotics would be bleak. Prior to antibiotic discovery the majority of bacterial meningitis cases were fatal[1]; therefore, more people would die if antibiotics were ineffective. Without antibiotics, surgical procedures would not have advanced[2]. Their failure now would lead to a backwards step in almost all aspects of medicine. Patients would risk succumbing to infection after surgery, breaking bones or puncturing the skin. People with weakened immune systems (our bodies' own defence mechanism against infection) due to old age, cancer or viral infection would increasingly perish. This is scary before we even mention food security problems if animals became diseased. Unfortunately these threats could become a reality as troops of bacterial species, including *Staphylococcus aureus*, are withstanding antibiotic therapy raids.

Staphylococcus aureus is a bacterium which can cause a range of infections. It can live on the skin with no negative impact, trigger unpleasant rashes and boils, or inflict a serious infection such as meningitis and blood poisoning with lethal consequences. Fortunately deaths associated with bloodstream infections have reduced up to 63% after antibiotic introduction[3]. Around 30% of us carry *Staphylococcus aureus*[4], usually on our skin and in our nasal cavities. Whilst very few people exposed to the pathogen develop severe symptoms, it does mean that Staphylococci are disseminated in the population ready to ambush their next victims. A wide spectrum of disease has also been observed in domestic and wild animals[5] which have the potential to transmit the bacterium to humans. Humans can also pass it on to animals[5]. Therapy used to be effective but currently treatments are failing. Unfortunately this means suffering and death rates resulting from this bacterium are rising. This is a major problem. But why are these antibiotics now unsuccessful?

In 1928, Alexander Fleming discovered a mould that produced a natural antibiotic that prevented growth of *Staphylococcus aureus* which he called penicillin. Eleven years later saw the start of World War 2 and massive effort to produce large quantities of this antibiotic to cure wounded soldiers subsequently infected with a range of bacteria. As a result, many men were saved and penicillin became widely used. However, as one war ended, another was brewing – an army of bacteria had gathered together to fight against penicillin. They established The Antibiotic Resistance and found an effective weapon, an enzyme called penicillinase, which, like a pair of scissors, is able to cut penicillin, rendering it inactive. Records show that penicillinase was first known to be used by *Staphylococcus aureus* in 1944[5]; since, it has been passed on to ~95% of their species globally[5]. So, the battle was back on! Only this time, it was microbial warfare.

Methicillin, an antibiotic which has the same pharmacophore (the active part of a drug) as penicillin, was then created. Imagine a Christmas tree - this is the key component or the 'active part', if we think of it like a drug. We can add lots of different things to it: tinsel, baubles, stars, angels, beads, in

lots of different colours: blue, green, red…… These different components can be added or taken away to create lots of different effects, but underneath it all, it is still a tree. The same principle can be used with pharmacophores – lots of different chemical parts can be added or removed. What is so special about methicillin? It has been designed to withstand penicillinase and kill penicillin-resistant bacteria.

The bacteria were not about to surrender yet: an elite group fitter than the rest of the army, like the SAS, formed within The Antibiotic Resistance. They called themselves the MRSA. They discovered a special mecA gene: a code which when deciphered provided them with a set of instructions enabling them to disarm the drug. So, how did Ambrose become a member? Well, bacteria have evolved several mechanisms to transfer DNA made up of lots of gene codes between each other, and like humans exchanging ideas, the most useful ones are kept circulating. A member of the MRSA was simply able to pass Ambrose a *mec*A gene, armouring him against methicillin.

But where did the *mec*A gene come from? No-one is really sure[6]. Perhaps the code was naturally accessible. Nutrients are limited in the environment. Bacteria, moulds and other microbes have to compete for these nutrients. Some deploy antibiotics to kill off their rivals; however, they must tolerate their own venom, and one way of doing this is carrying the information to decode it[7]. Thus, for every natural antibiotic produced, a set of guidelines to defuse it are possibly present in the environment. It only takes one bacterial spy to extract and pass on this information for bacteria to become resilient. This data distribution is scientifically known as horizontal gene transfer. There are several forms like phone, e-mail and post, and it is the method used to send messages, such as the antibiotic deactivation cyphers, between, or to other, microbial species.

Resistance can arise through another natural process: mutation. Mutations are basically errors made in the codes when bacteria copy them. Most translate the code to gobbledygook and the bacteria die. Sometimes, they are extremely helpful. Whilst antibiotics kill most bacteria, they startlingly also select for those that are the most dangerous[2] – those with mistakes that spell antibiotic survival. The lucky few, tough enough to endure antibiotic exposure, thrive because they suddenly have access to plenty of uncontested nutrients! Bacteria have a rapid replication time and multiply exponentially (1, 2, 4, 8, 16, 32, 64, 128…), so can soon generate a sizeable armed force, although, with maintained efficient antibiotic use, even they will die off before mass deployment. However, if an antibiotic course is stopped early, or is ineffective, these bacteria can dominate with dangerous consequences, so it is vital you take your antibiotics as prescribed! Furthermore, through mutations, bacteria can perfect horizontally-transferred genes to enhance their knowledge about antibiotic deactivation.

Whether by theft or chance, the *mec*A gene was obtained. The Antibiotic Resistance were victorious once again. So we reloaded with the new antibiotic vanomycin. Unfortunately the VRSA (vanomycin resistance *Staphylococcus aureus*) retaliated. Alas, our ammunition is now running low; we have very few useful medications to treat bacterial infections in reserve. Scientists are presently in pursuit of new antibiotic compounds, but the assignment is lengthy. It takes many years to discover new medications and get them safety approved, so our defences could be down for some time.

Negligence on our part has helped establish The Antibiotic Resistance. In a modernised world we've selfishly pumped chemicals out into the landscape. Basically, we've exposed bacteria to sub-lethal levels of poisons, giving them opportunity to concoct an antidote. Overuse and incorrect dosing of

antibiotics present the same problem. These issues potentially increase the likelihood of bacteria being able to put up a decent battle to previously seen or unseen antibiotics in the future[8]. Carefree hygiene approaches also mean harmful bacteria inhabit our homes and reside on our bodies. To reduce the risk of antibiotic resistance, attitudes need to change. People have to realise antibiotics will not cure their virus infection and prevention, such as hand washing, is better than cure. This would buy us more time to find drugs.

Worryingly over the years, The Antibiotic Resistance have recruited numerous species including *Escherichia coli*, *Mycobacterium tuberculosis* and *Clostridium difficile*. They have also occupied many settings including hospitals, farms, schools and public transport systems on a global scale. Chances of contracting untreatable infections are undoubtedly getting BIGGER. The threat from The Antimicrobial Resistance is eminent. It endangers our lives and life as we know it.

Meanwhile, back in the hospital, Ambrose had multiplied to create the Ambrosia. They infiltrated the toilets, light switches, door handles and fruit bowls, then hitch-hiked from patient to patient. As a deluge of people began to vomit, groan and faint, staff prescribed methicillin. Only, it didn't work. Next they tried vanomycin, but the VRSA had backed up. Reserve medications were injected into the heat of the battle. Some patients improved. Others continued to decline. Nothing could be done. They died. This is the threat that awaits us as more bacteria resist antibiotics.

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