Understanding the basics of

Antimicrobial Resistance

1- An historic perspective

This series of columns has been designed to give you a solid background knowledge on antibiotics so that you will be in a better position to appreciate the science behind issues of the moment, such as antibiotic resistance.

Let us start by considering the history of antibiotics and what antibiotics are. We will use the word antibiotic, but in most contexts this can be inter-changeable with antimicrobial.

Antibiotics are selective poisons in that at a certain dosage they kill the bacteria but do not harm the animal being treated.

Many centuries ago in Egypt, China and South America moulds were used to successfully treat infected wounds. We now know that it was not the mould, but the antibiotic(s) they produced that gave the desired effect. In the late 1880s antibiotics were starting to be identified but it was not until the 1940s that they became commercially available. The first one was penicillin.

Antibiotics and intensification

By the 1950s, with the intensification of pig and poultry production, antibiotics were found to enhance animal performance and these were originally referred to as antibiotic growth promoters or, more recently, as antimicrobial growth enhancers. Thus, in the livestock sector antibiotic usage fell into two distinct areas – the treatment of diseases and performance enhancement.

Not surprisingly, antimicrobial growth enhancers often worked better on the least well managed farms were subclinical diseases, including enteric dysbacteriosis, were more prevalent.

As soon as antibiotic usage became commonplace, an associated phenomenon – antibiotic resistance – emerged.

This was seen both when antibiotics were used in man or in animals.

As some of the key antibiotics that were used in man were also used in animals, a debate started in the 1960s which has continued to the present day.

That debate centres around whether the agricultural use of antibiotics contributes in any way to the emergence of antibiotic resistant organisms that cause disease in man.

Common misunderstanding

It is worth noting that although in everyday language we talk about antibiotic resistance in man and animals, what we really mean is antibiotic resistance in the bacteria which cause disease in man and animals.

In the late 1960s this issue came into the political arena in the UK and the resulting Swann Report (1969) recommended that antibiotics used in human medicine should not be used as growth promoters in animals.

This advice was followed by some countries, including the UK, but ignored by others. The debate rumbled on and in 1998 Denmark banned the use of in feed antibiotics.

In some sectors, such as poultry and pigs, this was accompanied by an upsurge in enteric disorders accompanied by a dramatic increase in the therapeutic antibiotic, amoxicillin.

The debate intensified in Europe and new facets such as vancomycin resistant enterococci came to the fore, with the result that within a few years the EU banned the use of all in-feed antimicrobial growth enhancers.

Since, then the debate has focused on fluoroquinolones and certain cephalosporins and these are now subject to industry codes of use in many countries.

Future columns will consider antimicrobial resistance in more detail. ■

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Antimicrobial Resistance

2 – Correct usage of antibiotics

This series of columns has been designed to give you a solid background knowledge on antibiotics so that you will be in a better position to appreciate the science behind issues of the moment such as antibiotic resistance.

One of the things that can predispose to the emergence of antibiotic/antimicrobial resistance is incorrect usage of the antibiotic that results in the survival of one or more of the target bacteria.

These bacteria then have the potential to develop resistance and, if they do so, their survival will be favoured the next time the same antibiotic is used and the resistant bacteria may then become the dominant form of that particular bacterium in that animal.

There are three key ways that this scenario can arise, as detailed below:

Incorrect antibiotic choice

There is a whole host of factors that the veterinarian has to take into account when choosing which antibiotic to use in a particular disease situation. The correct choice maximises the likelihood of a successful treatment outcome. Thus, it is important to seek, and then follow, your veterinarian's advice on antibiotic choice and usage.

Incorrect antibiotic dosage

Use of an antibiotic at a lower dosage than that intended can favour the emergence of resistance. If we weigh out antibiotic for feed or water administration we must be sure that this is done accurately. In addition, for water medication it is important to know what volume of water the weighed amount of antibiotic goes into.

If, for example, we have assumed that our 50 gallon tank was a 40 gallon one then we have a significant unintended dilution of the antibiotic in the water. When we calculate how much antibiotic to use we must double check the calculation (which many do) and the basic measurements on which the calculation is based (which many overlook). Are you sure that you know the volume of your water tanks?

As an alternative, many now use dispensing dosage pumps – their accuracy needs to be regularly checked. In a similar way, if we underestimate the weight of an animal that is going to be injected, we can unintentionally underdose it with antibiotic

Incorrect length of treatment

Getting the correct amount of antibiotic into an animal requires administering it at the correct dosage for the correct number of days. If we shorten the period of treatment then some of the disease causing bacteria can survive with an increased possibility of antibiotic resistance emerging.

A common mistake, be it with animals or humans, is to assume that because there has been an improvement in clinical signs we can stop the treatment. If we do this we increase the possibility of bacteria surviving the treatment and increase the likelihood of antibiotic resistance emerging. In addition, for many diseases this scenario also favours the occurrence of relapses.

In order to minimise the emergence of antibiotic resistance we must choose the correct antibiotic and use it at the correct dose and for the full prescribed period.

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Antimicrobial Resistance

3 – How has it arisen?

Although antimicrobial resistance can include other organisms, such as viruses, yeasts and protozoa (and a good example of the last of these is malaria), we will focus just on antimicrobial resistance of bacteria. This is also known as antibiotic resistance and is an important issue in the livestock sector.

Bacteria are constantly evolving and this enables them to efficiently adapt to new environments. As the generation interval (the time interval between the same point of development in successive generations) for bacteria can be as low as 10 minutes, evolution can be relatively quick compared to man where the generation interval is typically 20-30 years.

Selection of resistant strain

Antibiotic resistance is the ability of a bacterium to grow in the presence of a chemical (antibiotic) that would normally kill it or limit its growth. At the same time the antibiotic is working effectively against the non-resistant or sensitive strains of the same bacterium at the same location. That is, the antibiotic medication favours the resistant bacteria and these will ultimately dominate the scene – often monopolising it and displacing their sensitive counterparts

Antimicrobial resistance makes it harder to eliminate an infection from the body which, in effect, means the antibiotic becomes less effective. As a result, some infectious diseases are now more difficult to treat than they were just a few decades ago.

As more microbes become resistant to antimicrobials, the protective value of these medicines is reduced. Overuse and misuse of antimicrobial medicines are among the factors that have contributed to the development of drug-resistant microbes.

Genetically encoded

This resistance is encoded in the bacterium's genetic profile and genes and this conveys the resistance to the bacterium's progeny. Many of these genes tend to be antibiotic or antibiotic group specific. Interestingly, some of these genes have been found in bacteria taken from samples that were over 100 years old, that is, from the pre-antibiotic era, or from very remote locations, for example deep in the jungle or arctic tundra where antibiotics have never been.

This begs some interesting questions. Had the antibiotic been produced previously by Nature and induced bacterial resistance? Or, had that bacterium responded to a different stress in the same way it now responds to the antibiotic in question?

Be careful!

One thing this does mean is that we should be careful about the significance we place on any antibiotic resistance gene we find in a bacterium today because it may not have arisen from the recent use of that specific antibiotic! Does this scenario also apply to the occurrence of that gene where we would not expect it to be, or has the gene carrying bacterium been introduced into that situation? In other words, we should keep an open mind about what has caused the occurrence of a particular resistance gene in a particular bacterial population.

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4 – How does it occur?

In simple terms, in any population of bacteria there are likely to be some resistant ones. When the animal is treated with an antibiotic many bacteria, including those causing the disease (pathogenic bacteria) and good bacteria which protect the body from infection, are killed. This leaves the door open for antibiotic resistant bacteria to grow and multiply and become the dominant bacteria and take over. If the antibiotic resistant bacteria are pathogenic, the antibiotic will not kill them and the animal succumbs to the disease and can die.

How do antibiotic resistant bacteria arise in the first place? All genetic material occasionally and spontaneously randomly mutates. On many occasions this is of no consequence but very rarely it will throw up a genetic change of consequence to the bacterium such as the conferring of antibiotic resistance, enhancing virulence or, as probably occurred with Salmonella enteritidis in poultry, make it more invasive. Mutation is a relatively rare event but it appears to occur more frequently in bacteria because of their relatively short generation gap. Mutation occurs when the bacteria are replicating and one mutation occurs every 100,000,000 replications.

The antibiotic resistance becomes encoded in the bacterium's genes and is passed down to the bacteria's progeny bacteria who are then also resistant. Occasionally a bacterium can reproduce by conjugating (mating) with another of a closely related bacterial species. When this happens the bacterium receiving the genetic material often only incorporates a few genes of the donated genetic material into its genetic material and if those genes contain one for antibiotic resistance then the resulting progeny will be an antibiotic strain of the same type as the 'mother' bacterium. This might occur with the result that a non-pathogenic bacterium with an antibiotic resistance gene passes that gene on to a pathogenic bacterium such as salmonella.

Sometimes bacteria become resistant to more than one antibiotic. This phenomenon is known as multidrug resistance and bacteria with it are sometimes referred to as superbugs. Occasionally a particular combination of pathogen and bacterium give rise to a more frequently arising resistance. Examples of this include methicillin resistant Staphylococcus aureus, which is commonly referred to as MRSA.

Occasionally antibiotic resistant bacteria are transmitted from animals to man by the consumption of products derived from animals, by close or direct contact with animals or through the environment. The evidence supporting transfer of macrolide resistant bacteria from animals to man is very scant and most of the evidence shows that pathogens of concern to man arise in man and remain there.

There are four main mechanisms by which bacteria exhibit resistance to bacteria. These are:

1. Drug inactivation or modification.

2. Alteration of the target site on/in the bacterium for the antibiotic.

3. Alteration of a metabolic pathway in the bacterium.

4. Reduced antibiotic accumulation in the bacterium.

These four mechanisms will be considered further in the next issue.

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5 – Intrinsic or acquired in nature?

Sometimes a bacterium can survive antibiotic treatment and multiply because it is intrinsically resistant. A good example of this can be seen when an antibiotic, such as penicillin that prevents cell-wall building, can not control a bacterium that does not even build a cell wall (Gram negative bacteria). This is known as intrinsic resistance.

Bacteria are also able to acquire resistance. This occurs when a bacterium changes in such a way that it is protected from the effects of a particular antibiotic. Such resistance can be gained in one of two ways – through a new genetic change that helps the bacterium survive or by getting DNA (genetic material) from another bacterium that is already resistant. This is acquired resistance.

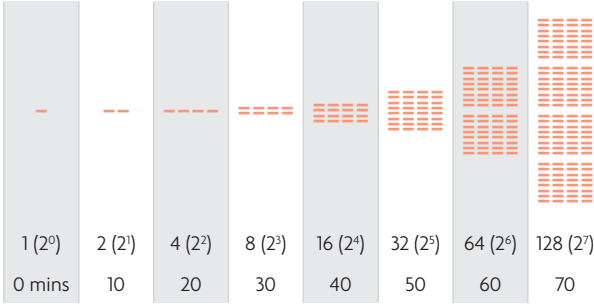
DNA provides instructions to make proteins, so a change in DNA can cause a change in a protein. Sometimes this DNA induced change is a structural one. If this occurs at the site on the protein where a particular antibiotic acts, that antibiotic may no longer be able to identify the position at which it acts on the bacterial protein and so can not work. This may prevent the antibiotic from entering into the bacterial cell or prevent it working once it is in the cell.

As soon as such a change occurs it can spread through a bacterial population by reproduction or DNA transfer. This is greatly helped by the fact that bacteria are very good at sharing genes, including genes for antibiotic resistance. They can share resistance genes that have been in the population including those with new genetic changes.

When a bacterium with an antibiotic resistance gene gives a copy of that gene to another bacterium the process is known as lateral gene transfer.

However, there are other mechanisms by which bacteria can transfer DNA. For example, bacteria can be infected by a type of virus known as a bacteriophage. As part of its life cycle, the bacteriophage assimilates bacterial DNA and when it dies, this DNA, which may include some antibiotic resistance genes, is released and can be taken up and used by other bacteria.

Remember this occurs relatively quickly in bacteria as their generation interval can be as short as 10-12 minutes.



The diagram above is a diagrammatic representation of bacterial multiplication by binary division. In a 24 hour period a bacterium with a 10 minute life cycle can go through 144 generations. One bacterium becomes 2 (2^1), then four (2^2), then 8 (2^3), then 16 (2^4) and so on. At the end of the day 2^{144} offspring have been produced (a huge number). Man, with a generation interval of 25 years, would take 3,600 years to produce the same number of progeny a bacterium can produce in a day!

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6 – Reflections on MRSA

MRSA stands for methicillin resistant Staphylococcus aureus and it is a type of Staphylococcus aureus bacteria that is resistant to several antibiotics, including methicillin. The importance of this is that, for some serious infections in man where the causative bacterium has multiple antibiotic resistance, methicillin is an antibiotic of last resort. If the causative bacterium was therefore to also have methicillin resistance there would be no treatment options.

In man, MRSA is often associated with skin infections but, in some instances, it causes pneumonia and other issues. If left untreated, MRSA infections can become severe and cause sepsis – a life-threatening reaction to severe infection. In hospitals or nursing homes, MRSA can cause severe problems, such as bacteraemias, pneumonia and surgical site infections.

Methicillin resistance, including MRSAs, have been seen in a wide variety of animals but the significance of this in relation to human health is not fully understood and is probably minimal.

There is very little evidence of MRSAs moving from animals to man and, to the contrary, there is mounting evidence to support the theory of host specific Staphylococcus aureus strains including MRSAs that do not move between specific animal species and man.

However, where these strains can commingle there is always the possibility of transference of methicillin resistance.

Considering the aforesaid, it can be seen why MRSAs have become a political hot potato. If doctors can convince consumers and politicians that animal origin is really important, it takes the spotlight off their shortcomings, for example in relation to nosocomial infections in hospitals.

Needless to say, veterinarians are happy for the spotlight to stay on their human counterparts. Thus, science becomes interlaced with public opinion and politics, which is a very dangerous mix!

Interestingly, it has recently been discovered that people with the rival bug Staphylococcus lugdunensis in their nostrils were less likely to have Staphylococcus aureus. It would appear that this bacterium has a gene that encodes for building a new antibiotic – lugdunin.

Tests on mice have shown that lugdunin could treat superbug infections on the skin, including MRSA, as well as Enterococcus infections.

By introducing the lugdunin genes into a completely innocuous bacterial species we hope to develop a new preventive concept of antibiotics that can eradicate pathogens. This means that, one day, people could be infected with genetically modified bacteria to fight their infections.

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7 – FAO Viewpoint

The Food and Agriculture Organization of the United Nations (FAO) views antimicrobial resistance (AMR) as a major global public and animal health issue. The risk appears to be particularly high in countries where legislation, regulatory surveillance and monitoring systems regarding the use of antimicrobials and the prevention and control of AMR are weak or inadequate.

FAO plays a key role in supporting government, producers, traders and other stakeholders to adopt measures to minimise the use of antimicrobials and to prevent the development of AMR.

FAO works on antimicrobial resistance with its international partners (WHO and OIE) and also with other partners, as appropriate.

The 39th Session of FAO's Governing Conference has called for urgent action at both the national and international levels to respond to the growing threat of antibiotic-resistant pathogens in the world's food producing systems – terrestrial and aquatic.

AMR is an increasingly serious threat to public health and sustainable food production that requires a response spanning all sectors of government and society, according to a resolution adopted by the Conference in 2015 (see Resolution 4/2015 in the report of the Conference). The resolution flags as an urgent concern growing levels of AMR in disease- and infection-causing micro-organisms, as they become less responsive to treatment, making infections or diseases more difficult, or impossible, to cure.

To guard against AMR and as part of overall efforts to reduce hunger, FAO helps countries develop and promote:

- Good hygiene practices to control the spread of resistance through food.
- Attention to risk of AMR by Codex Alimentarius.
- Efficient livestock husbandry for healthier, more productive animals.
- Guidelines for prudent use of antimicrobials in aquaculture.
- Good animal health and management practices including improved biosecurity and use of vaccines instead of antimicrobial drugs.
- Policies and capacities for responsible antimicrobial use.
- Health management approaches that recognise the links between animals, humans and ecosystems.

AMR represents an increasing global concern for the agriculture sector. The very microbes that cause infections and disease are becoming resistant to antimicrobial drugs because of overuse, misuse and counterfeiting. The more these drugs are abused, the greater the likelihood that microbes will become resistant, thereby placing livestock and livelihoods at risk.

Prudent use of antimicrobials in livestock and aquaculture is essential in light of the increased demand for animal proteins by a rapidly growing world population expected to exceed 9.6 billion by 2050. Intensifying production means additional challenges in disease management and even higher potential for increased AMR.

AMR can be tackled by working closely with veterinarians, farmers, feed and food producers and food safety professionals, to support best animal health and production practices which underpin the prudent use of antimicrobials.

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8 – Reservoirs of resistance

Antibiotics are derived from substances that were developed thousands or maybe millions of years ago to protect bacteria from adversities. The bacteria that were affected by these antibacterial substances often developed resistance against them.

Some of these substances were later used to develop antibiotics and the resistance that was created thousands of years ago was just as effective against the new antibiotic of similar structure. It was then a matter of chance when the new antibiotic came across a bacterium containing such a resistance gene. It was really bad luck if it was present in the particular pathogenic bacterium that the new antibiotic was to be used against.

However, since the original resistance was created a long time ago and considering the very short generation time for bacteria, such resistance could become quite widespread in different bacterial populations. The first time the scientists discovered a particular resistance gene was when they were investigating a modern day resistance problem and it was named accordingly. If we examine bacteria that could never have come across antibiotics, such as those found deep in arctic soils or in corpses that have been buried for hundreds of years, these genes can be found confirming their origin was from before the time the antibiotic was created.

Thus, many bacteria could contain a resistance gene that is waiting for the opportunity to move into a modern day pathogen.

There are various populations of such bacteria. Obviously, there are human and animal bacteria, then there are those in home or hospital or farm and veterinary practice environments. There are the populations of bacteria found in the soil and water supplies as well as those found in sewage and other effluents. Each of these groups of bacteria represents a reservoir of resistance that modern day pathogens can tap into!

If we look at particular examples we can see how a resistance gene started in an animal population and then moved into a human population only at a later date to move back into the same or a different animal population. As time progresses this complex picture will be slowly elucidated.

In the meantime, what can we do to lessen the likelihood of more antibiotic resistance emerging? One obvious and worthy strategy is to minimise the contact between the bacterial population in our animals and these other bacterial populations. This may be possible in modern housed intensive farming but it is a virtual impossibility in outdoor or free range production.

Once again, we have the situation of what the consumer wants (free range production) potentially giving him another issue (antimicrobial resistance) that he does not want!

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