National Office of Animal Health

Antibiotic Resistance

Summary

This briefing document considers the topic of antibiotic resistance and discusses important issues including the development of resistance and its significance for human and animal health. The future outlook for antibiotic resistance is also highlighted in light of current proposals and policy measures.

Overview

Antibiotics (anti-bacterial compounds) have a direct action on bacteria and are used for the treatment or prevention of infection in people and animals. There are however a number of possible outcomes when bacteria are exposed to an antibiotic. Bacteria can be killed, they can be weakened – making them easier for an animal's own immune system to kill them or they can remain unaffected, or 'resistant'.

The actual outcome depends on a number of factors including whether the antibiotic is the correct type to work against that bacteria – as not all antibiotics kill or weaken all bacteria. There are different classes of antibiotics and even within each class, there are a number of different antibiotics. It is therefore important to remember that bacteria may not be killed if an inappropriate antibiotic type (one that does not target that bacteria) is used.

Bacteria can also show reduced susceptibility or resistance to a particular antibiotic(s). Antibiotic resistance is defined as the ability of a micro-organism to grow or survive in the presence of an *antibiotic* that is usually sufficient to inhibit or kill micro-organisms of the same species (1). The term antimicrobial resistance, or AMR, is also commonly used to mean antibiotic resistance, although AMR technically refers to resistance to *any compound* with a direct action on micro-organisms used for treatment or prevention of infections. So antimicrobial resistance is a broader term than antibiotic resistance.

Bacteria that are resistant to one class of antibiotic are not automatically resistant to all classes of antibiotic.

However, some bacteria can be resistant to more than one antibiotic class. When bacteria are resistant to a number of bacteria they are called multi-resistant and although there is no internationally agreed definition of what constitutes multiple resistance, a recent report from the UK veterinary medicines regulator the Veterinary Medicines Directorate (VMD) defined multiple resistance as resistance to four or more antibiotics (2).

To minimise conditions which may favour the development of antibiotic resistance and to reduce the chances of treatment failure, it is important that antibiotics are taken correctly, following the instructions for dosage and duration of treatment. Some antibiotics need to reach a particular concentration in the body (concentration-dependent) or are provided for a certain length of time (time-dependent) in order to be fully effective. Importantly, sub-optimal dosage or duration of antibiotic treatment are important contributors to the development of resistance. This is why it is essential that treatment doses are calculated correctly and that the treatment duration instructions are followed exactly as directed by the vet who prescribed the antibiotic.

Origins of Antibiotic Resistance

Antibiotic resistance is an ancient, biological phenomenon (3, 4). A growing body of evidence shows that antibiotic resistance evolved alongside antibiotic production in the natural environment (4). Long before the introduction of modern antibiotics, bacteria developed mechanisms to survive the effects of natural antibiotics produced by bacteria and fungi in the environment. Resistance genes have been detected in 30,000 year old ancient Alaskan soil sediment samples, which researchers say "*firmly establishes that antibiotic resistance genes predate our use of antibiotics and offers the first direct evidence that antibiotic resistance is an ancient, naturally occurring phenomenon widespread in the environment*" (3).

The reservoir of natural resistance genes is not confined to soil samples. Studies of people living in

remote locations e.g. hunter-gathers in the Amazon, with no known exposure to antibiotics have found functional antibiotic resistance genes (5). The implication of these findings is that resistance to antibiotics cannot be fully eradicated. However, greater knowledge of the spectrum of resistance mechanisms that exist in nature could help us to predict the potential success of any new antibiotics (4).

Mechanisms of Antibiotic Resistance

Bacteria can be susceptible to antibiotics, they can have intrinsic/natural resistance to antibiotics or they can develop acquired resistance to antibiotics.

Intrinsic resistance is the natural ability of bacteria to resist the effects of an antibiotic due to inherent structural or biochemical features of the bacteria e.g. if an antibiotic is too large to cross the cell wall of a bacteria and get access to its target within the cell. Knowing which bacteria were never susceptible or have a natural resistance to particular antibiotics helps vets and clinicians to prescribe appropriate and effective treatments.

Resistance to antibiotics can also be acquired either from the result of mutation of bacterial genes involved in normal physiological processes and cellular structures. These genetic mutations are changes in the DNA sequence of bacteria that occur continuously, to varying degrees. Bacteria can also become resistant through the acquisition of foreign DNA originally from other bacteria, e.g. via plasmids (small circular DNA strands), in a process called Horizontal Gene Transfer (HGT).

Sometimes these genetic mutations or the acquisition of foreign resistance genes can lead to the emergence of bacteria with an improved ability to survive treatment with particular antibiotics. If those bacteria are then exposed to these antibiotics they increase in numbers, while the more susceptible bacteria are killed off. Bacterial population changes are inevitable without the careful management of antibiotics used against them and, as explained above, will occur more quickly if antibiotics are not taken in accordance with their prescribing instructions.

Resistance Development and Dissemination

The rate at which resistance develops is difficult to predict and depends on many factors related to both the particular bacteria and antibiotic in question.

Nevertheless, the inappropriate use of antibiotics can accelerate the rate of resistance development. Inappropriate use means using antibiotics for the wrong reason e.g. for viral infections or using them incorrectly e.g. a lower dose or altering the frequency of dosing. This can result in the antibiotic not reaching the correct concentration or not being present for long enough, potentially allowing some bacteria to survive.
There is still much that is unknown about what happens to antibiotic resistance after it has developed. Current research and surveillance aims to identify and quantify the sources and relative contributions of antibiotic resistance to the human clinical resistance problem. To date, it is believed that the main driver of clinical resistance in people is inappropriate use of antibiotics in people, as stated in the UK government five year antimicrobial resistance strategy 2013-2018 "*Increasing scientific evidence suggests that the clinical issues with antimicrobial resistance that we face in human medicine are primarily the result of antibiotic use in people, rather than the use of antibiotics in animals*" (6).

Food of animal origin is also being examined as a possible source of resistance, which might cause clinically relevant antibiotic resistant disease in people. Recent surveillance and research work in Denmark comparing the bacteria that cause septicaemia/blood infections in people and those from animal origin, using sophisticated molecular analysis, concluded that "*consumption of meat may currently be considered an insignificant source for human the infections*" (7).

In Great Britain, studies have examined a particular type of resistance caused by the production of ESBLs or extended spectrum β-lactamases, which are enzymes that cause resistance to the beta lactam classes of antibiotics. This research has shown that ESBLs in *E.coli* bacteria of chickens and turkeys were found not to be the major source of infection causing disease in people (8, 9). Another study, also looking at resistance in *E.coli* in people and animals in the UK, Germany and the Netherlands found that only 1.2% of the samples from animals were similar to those from people, although many human samples from the three countries were highly similar, highlighting the importance of minimising human-to-human transmission in controlling the spread of ESBL-positive *E.coli* (10).

This research highlights the complexity of resistance and challenges the misconception that resistance in animals is a major contributor to clinical disease in people. Nevertheless, people and animals share the same ecosystems, therefore we all have a responsibility to ensure best practice in antibiotic stewardship is observed. In an increasingly connected world, the international movements of people, animals and food are also important considerations when assessing the relative risk of resistance development and dissemination.

Measurement of Resistance

The ability of bacteria to survive in the presence of an antibiotic can be measured in the laboratory. Changes in the susceptibility of bacteria can be monitored in the laboratory, by measuring their ability to grow in the

presence of an antibiotic. Bacteria can display a spectrum of responses to the antibiotics tested ranging from being fully susceptible, to less susceptible to resistant.

It is important to understand that there are a number of different ways in which antibiotic resistance or reduced susceptibility can be measured in the laboratory. This must be taken into consideration when attempting to meaningfully interpret data in reports from a range of sources that use different methods.

The Minimum Inhibitory Concentration (MIC) is the minimum concentration of antibiotic which will inhibit the growth of the bacteria. When bacteria become less susceptible to an antibiotic, the MIC will increase. These measurements, along with clinical factors, provide very practical information to help veterinary surgeons and clinicians decide on an appropriate antibiotic therapy.

Medical professionals need to know that when they choose an antibiotic to treat a specific infection it is likely to be effective. The MIC, which is determined in the laboratory, can be compared to a cut-off value called a Clinical Breakpoint (CBP). If the MIC is below this CBP value, then a successful clinical response is expected if the antibiotic is given as recommended. CBPs are not available for every antibiotic and bacterial combination.

Epidemiologists that are interested in studying populations of bacteria use another value, called an epidemiological cut-off value (ECV), to determine when wild-type/susceptible bacteria begin to show reduced susceptibility. However, when bacteria have an MIC greater than the ECV, and show reduced susceptibility, they may yet respond to clinical treatment - as reduced susceptibility does not always mean clinically relevant resistance. CBPs may therefore be a more appropriate value to use when we want to understand clinical resistance that impacts the success of antibiotic therapy in animals and people.

The methods by which we measure resistance must be considered when attempting to meaningfully compare data and also when interpreting the significance of the data for clinical success.

Human and Animal 'One Health'

There is a well-recognised clinical crisis in human medicine where antibiotic resistance is making some bacterial diseases more difficult to treat with antibiotics. Examples of important bacterial disease include multidrug resistant *Mycobacterium tuberculosis* (MDR-TB) and hospital-acquired infections, including bloodstream infections (11).

Advances in medicine have increased the numbers of vulnerable patients, e.g. the very young or old, which may have underlying disease or immunosuppression. These patients, who are brought together in specialist hospital units, are prone to infection by opportunistic bacteria, which would normally be harmless to healthy individuals, and these progress to develop resistance (11). Resistant bacteria can then spread between people through person to person contact in hospitals and the wider community. Environmental reservoirs are an important vector in hospitals (12). In addition, international travel can facilitate the spread of resistant bacteria from regions where antibiotic use is poorly regulated (11).

A contrast exists in the animal health sector where, as stated by the UK's VMD, "*at present, disease in animals, which is untreatable by antibiotics authorised for veterinary use is still rare*" (2). In fact, as recently highlighted in the annual progress report on the UK government AMR strategy "*clinical resistance is rare in animal health in the UK and resistance in key veterinary zoonotic micro-organisms (that can cause disease in humans) are generally among the lowest in the European Union (EU)*" (13). Safeguarding the continued health and welfare of our animals, by working to ensure clinically relevant veterinary resistance continues to be a rarity, is a key priority for the animal health sector.

Despite the different challenges in the human and veterinary sectors – animals, people and the environment all form part of a complex and interconnected ecosystem. Understanding and addressing antibiotic resistance, should therefore be approached from a 'One Health' perspective.

Examples of key 'One Health' bacteria include the food-borne pathogens e.g. *Salmonella* and *Campylobacter*, which occur naturally in animals without necessarily causing disease. Infections in people frequently do not require treatment with antibiotics. Another important One Health bacteria is *E. coli*, which mostly lives as a commensal in the gut of people and animals and is the most common bacteria to cause infections in people (12).

Our understanding of the ecology, sources and spread of resistance is improving with the development of ever more sophisticated molecular genetic and biological data analysis techniques, which can allow rational targeting of effective measures against antibiotic resistance.

A study by Mather and colleagues challenged views that promoted the contribution of local animal reservoirs as a suspected source of *Salmonella* and antibiotic resistance in people (14). Mather's study used an unprecedented national collection of isolates collected contemporaneously from humans and animals in Scotland and included a sample of internationally derived isolates. Contrary to conventional understanding, they demonstrated that *Salmonella* and its resistance genes were largely

maintained within animal and human populations separately and that there was limited transmission in either direction (14). The authors stated that *'the majority of human infections in Scotland were unlikely to have been sourced from the local animal population'* (14). The study not only highlighted the importance of challenging the status quo when scientific advances allow, but more importantly it focused attention on the more probable sources of clinically relevant resistant *Salmonella* in people such as foreign travel, imported food and environmental reservoirs (14).

Nevertheless, surveillance of resistance is an important activity in furthering our knowledge and understanding of antibiotic resistance, or as it is often called, antimicrobial resistance (AMR). Although, AMR is a broader issue than bacterial antibiotic resistance, which is the main concern for human health. Encouragingly, as stated in the progress report on the UK government AMR strategy "*In animal health, we are undertaking the most extensive surveillance in Europe on AMR veterinary pathogens. In addition, for food borne pathogens the statutory surveillance programme has been expanded*" (13). With greater participation and widening of important surveillance initiatives, it will become increasingly relevant to adopt a sound scientific approach to inform responsible practices and formulate evidence-based policies around antibiotic use.

Current Efforts and Future Outlook

Safeguarding the future effectiveness of antibiotics as vital medicines for animal and human health is widely regarded as a critically important endeavour. To achieve our common goals, considerable efforts are being made to coordinate and collaborate on initiatives in the animal and human sectors, addressing our responsibilities in a 'One Health' approach (15).

Antibiotic resistance, as a spontaneous, naturally-occurring phenomenon, will continue to occur in bacteria – both towards old, established antibiotics and to any new antibiotics developed in the future. Eradicating antibiotic resistant bacteria is therefore impossible, but we can work towards limiting resistance development through responsible and appropriate antibiotic use.

Attention has focused on the spread or dissemination of resistant bacteria between people, animals and the environment. It is important to understand the drivers behind the growing clinical problems in human medicine and it is easy, yet unscientific and non-evidence based, to directly equate resistance and use of antibiotics in animals with the clinical problems seen in people. We already know that the main driver for resistance in people is antibiotic use in people and it is becoming increasingly apparent, with the advancement of DNA analysis technologies, that assumptions on the spread of resistance can be incorrect.

Going forward, measures to tackle the human clinical resistance issue must be built on evidence gained from sound science. Throughout the EU, continued harmonisation and capture of surveillance data has been important to provide baseline data on resistance, or reduced susceptibility, in key bacteria. Yet this data constitutes only one aspect of the complex ecology of antibiotic resistant bacteria. Building on the usefulness of this data in the future will be dependent on further state-of-the-art research that accurately captures the relative contributions of all sources of resistant bacteria in human clinical infections resistant to treatment. Multidisciplinary co-operative research could also shed light on critical control points in resistance dissemination to further our understanding of antibiotic resistance epidemiology.

The development of new antibiotics is often proposed as part of the solution to antibiotic resistance, yet the research and development of antibiotics has stalled for many years. The situation is particularly precarious in the animal health sector, where severe disincentives exist in bringing a new antibiotic to market. Proposals in the EU draft veterinary medicine regulations mean that antibiotics initially developed by the animal medicines sector could at any stage in the future be reserved for human use only. The regulatory uncertainty, coupled with the inevitable development of resistance, limiting the effective lifespan of the product, has depressed investment in the research and development of new antibiotics for animals. Notwithstanding these important factors, the development of a new veterinary medicine takes a considerable amount of time (8 to 12 years on average) with significant costs.

Many of the antibiotics used in animal health are also used in human medicine and restricting veterinary use on those used for people would greatly limit treatment options for animals, adversely impacting health and welfare. There have been proposals to reduce antibiotic use in food production to an arbitrary level. This is counter-productive for a number of reasons. Reduction targets can lead to improper use of antibiotics, including shortened treatment durations or reduced dosage with potential consequences on animal welfare and resistance development. There is also a risk that in trying to reduce use in simple tonnage terms, more potent antibiotics, often the Critically Important Antibiotics (CIAs), could be used as they often have a lower dose rate in mg/kg.

Critically Important Antimicrobial are those antibiotics considered of greatest importance in human medicine by the World Health Organisation (WHO). The European Medicines Agency (EMA), which is responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU, has further categorised the WHO list of CIAs to guide the use of antibiotics in animals (16). Category 1 are

antimicrobials used in veterinary medicine where the risk for public health is estimated as low or limited, Category 2 are antimicrobials used in veterinary medicine where the risk for public health is estimated higher and Category 3 are antimicrobials not approved for use in veterinary medicine.

In the UK, sales of CIAs (fluoroquinolones and 3rd/4th generation cephalosporins) are already very low, at 0.2% and 0.12% of total antibiotics for food producing animals in 2014 (2). Removing these classes of antibiotics from the veterinary toolbox limits treatment options for animals and places more pressure on the remaining few antibiotics in terms of resistance development. Using a range of antibiotics licensed for veterinary use in a responsible manner reduces the resistance pressure on any one class of antibiotic and ensures animal welfare is not compromised in the process.

The key message of responsible use is acknowledged by the medical and veterinary professions. Indeed in the UK, Europe and globally, the animal health sector supports important initiatives promoting best practice in animal medicine use (1, 17). More information on the responsible use can be found in NOAH 'Responsible Use of Antibiotics' briefing document. Of course, the need for antibiotics to be prescribed in the first place can be reduced through preventative health measures including vaccine use, where available, and good biosecurity.

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What is NOAH?

The National Office of Animal Health Ltd represents the UK animal medicine industry: its aim is to promote the benefits of safe, effective, quality medicines for the health and welfare of all animals. For further information, including more briefing documents on animal medicines topics see www.noah.co.uk and follow @UKNOAH on Twitter. For more information on RUMA (the Responsible Use of Medicines in Agriculture Alliance), including responsible use guidelines, visit www.ruma.org.uk.

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