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Antibiotic resistance via the consumption of meat

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1. Introduction

"Antibiotics are among the most potent life-saving interventions in all of medicine." (Spellberg, B. et al, 2016). The broad range of use of antibiotics is overwhelming and can cover an array of medical complications from simple skin infections to very serious and life-threatening infections.[1] The availability and use of antibiotics is essential to enable critical medical advances, especially in areas such as oncology and organ transplantation.[2] Therefore, the importance of antibiotics in both human and veterinary medicine alike, is vital.

At the time of the discovery of penicillin in 1945, Alexander Fleming had exclaimed his concern about the overuse of antibiotics.[3] Fleming explained, "The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out." (Spellberg, B. et al, 2016). Since then, the abuse of antibiotics has become very severe, and in the last number of decades antibiotic resistance has become a very pressing topic within many sectors including; human medicine, animal medicine and the food industry. Antibiotic use in the food chain has the highest concern and is the lead factor in antibiotic resistance. The food chain is the origin of the cascade, that is producing terrifying consequences in both human and veterinary medicine.

Within recent years the subject of antibiotic resistance has been publicised by a number of governing bodies, such as the European Food Safety Authority (EFSA) and the World Health Organisation (WHO). These bodies have taken actions to create awareness and have implemented strategies in order to protect the public and prevent further resistance of vital antibiotics. They are faced with a never-ending battle in educating people at every level of the cascade. There is particular trepidation within the meat industry, which has seen a relatively high number of reported food-borne diseases associated with the consumption of meat produce. The overuse of antibiotics in this industry has stemmed from the belief that antibiotics increase production, with reduced costs.[4] This issue must be addressed immediately, via education and awareness through the governing bodies of every country.

[1] Spellberg, B. et al (2016). p.2
[2] Spellberg, B. et al (2016). p.2
[3] Spellberg, B. et al (2016). p.4
[4] Spellberg, B. et al (2016). p.4

These antibiotic resistant bacteria can spread between people, meaning the abuse of antibiotics isn't just affecting individuals but affecting the entire population and even future generations.[5] This raises serious issues in human medicine that need to be tackled immediately. The threat of regression in medical advances is existent and will have problematic consequences for human health, the concerns of which are especially heightened in the case of life-threatening diseases.

Parts of Europe, particularly the Western regions, have attempted to prevent the use of antibiotics in growth promotion and prophylaxis.[6] However, antibiotic resistance is a multifactorial issue that cannot be solved with one remedy.[7] A number of challenges face the governments and their promoting bodies; these include challenges in the fields of science, economics and also in the regulatory laws of each country. In other words, the issues of antibiotic resistance won't simply be solved by the manufacturing of new antibiotics.[8]

[5] Spellberg, B. et al (2016). p.3
[6] Spellberg, B. et al (2016). p.4
[7] Spellberg, B. et al (2016). p.3
[8] Spellberg, B. et al (2016). p.3

2. Materials and methods

This literature review is based on the materials I collected from different databases, websites and also journals. I used Google as my main search engine to obtain articles, journals and websites for my research. The main databases I used were NCBI[9], science direct[10], JSTOR[11] and Elsevier[12]. From these databases I gathered journals with the most relevance to my thesis topic, and I used them as the basis on which to structure and create my literature review.

I obtained ideas from websites on which particular areas of the topic I wanted to focus on the most. These websites included, the World Health Organisation (WHO)[13] and the European Food Safety Authority (EFSA)[14]. I wanted to focus mainly on the affects antibiotic resistance was having on public health via the consumption of meat and the most important antibiotics involved. I also accessed the websites of governments worldwide and specialised agencies to scope their views on the subject matter.

[9] https://www.ncbi.nlm.nih.gov/
[10] http://www.sciencedirect.com/
[11] http://www.jstor.org/
[12] https://www.elsevier.com/
[13] http://www.who.int/en/
[14] https://www.efsa.europa.eu/

3. Background

3.1 What is antibiotic resistance?

Antibiotics have been used for up to 70 years in human medicine to treat life-threatening diseases and to prevent rejection in organ transplantation.[15] However, due to the extensive overuse of antibiotics, resistance to them has developed.[16] Therefore, resistance occurs when an antibiotic loses the ability to effectively inhibit bacterial growth; the bacteria are resistant and continue to replicate even after the administration of therapeutic levels of the antibiotic.[17] Antibiotic resistance has been an ongoing concern for decades, and due to the inappropriate use of antibiotics, the problem is becoming even more accelerated in both human and animal medicine alike.

Resistance to antibiotics in food-producing animals can be spread to humans not only by food-borne routes but also via water, other contaminates in the environment and also through direct contact with animals.[18] The diseases caused by these resistant bacteria may result in the need for second line antibiotics, required when the previous antibiotics prescribed were unsuccessful due to antibiotic resistance.[19] Therefore, antibiotic resistance needs to be addressed in order to save this revolutionary medicine and the worlds health.

3.2 Mechanisms of antibiotic resistance

Antibiotic resistance can occur on the basis of genetics or mechanics. The majority of antimicrobial compounds are produced naturally, in the same surroundings as the bacterial agents. Hence, antibiotic resistance occurs due to the interactions between the bacteria and their environment, as they must evolve in order to survive; these are known as intrinsically resistant bacteria.[20]

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[15] CDC (2017)
[16] CDC (2017)
[17] Alliance for the Prudent use of Antibiotics. (2014).
[18] Food, E. & Authority, S., (2017). p. 25
[19] Food, E. & Authority, S., (2017). p. 25
[20] Munita, J.M. and Arias, C.A. (2016). p. 2

3.2.1 *Genetic antibiotic resistance*

An organism may be intrinsically resistant to a particular antibiotic but may also acquire resistance to other antibiotics.[21] Acquired resistance occurs on a genetic basis, due mutations in chromosomal genes or through the external acquisition of genetic elements of resistance.[22]

- *Mutational resistance*: A group of bacterial cells foster mutations in genes that affect the action of the antibiotic, leading to the survival of the cell.[23] The mutation can alter the activity of the antibiotic by one of the following mechanisms: modification of the target site, reduction in the uptake of the antibiotic, activation of efflux mechanisms or in the alteration of metabolic pathways.[24]

- *Horizontal gene transfer*: Horizontal gene transfer is the exchange of foreign DNA, containing antibiotic resistant genes between organism; in particular from intrinsically resistant bacteria.[25] This mechanism has had a leading role in antibiotic resistance, fuelling the evolution of bacteria.[26] Mechanisms of horizontal gene transfer include:

    - *Transformation:* Bacteria can obtain, incorporate and express fragments of foreign DNA from the environment.[27] Certain prerequisites are required for the occurrence of transformation; DNA must be present in the environment, the bacteria must be competent for the uptake of the DNA and the DNA must be stable.[28] Other bacteria are capable of completing the transformation of DNA when additional conditions are present which include; the presence of peptides, an appropriate nutritional status of the bacteria, a stressful environment and also interactions with antibiotics which, in other words, means antibiotics can bring about the transformation of their own resistant genes.[29]

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[21] Blair, J. M. A. *et al.* (2014). p. 42
[22] Munita, J.M. and Arias, C.A. (2016). p. 2
[23] Munita, J.M. and Arias, C.A. (2016). p. 3
[24] Munita, J.M. and Arias, C.A. (2016). p. 3
[25] Munita, J.M. and Arias, C.A. (2016). p. 3
[26] Munita, J.M. and Arias, C.A. (2016). p. 3
[27] Von Wintersdorff, C. J. H. et al. (2016). p. 3
[28] Von Wintersdorff, C. J. H. et al. (2016). p. 4
[29] Von Wintersdorff, C. J. H. et al. (2016). p. 4

- *Transduction:* The process through which bacteriophages move genes from one bacteria to another.[30] Bacteriophages are capable of transferring certain genetic components such as, chromosomal DNA, transposons, plasmids and genomic islands.[31] Some have a wide host range and can transfer genetic material even between taxonomic classes,[32] illustrating the severity of transduction in antibiotic resistance.

- *Conjugation:* Involves direct cell-to-cell interactions between two bacteria, resulting in the transfer of genes.[33] The interactions occurs via pili or adhesins located on the surface of the bacteria.[34] Mobile genetic elements (MGEs) which include, plasmids and transposons, are used in order to share the genetic information between organisms.[35] Conjugation is the most common method of gene transfer; granting protection from the environment, whilst having a wide host range.[36]

After the genes are transferred, rapid development of both the genes and the bacteria occurs. This evolution results in bacteria with a greater resistance and diversity,[37] intensifying the battle against antibiotic resistance.

3.2.2 Mechanical antibiotic resistance

Bacteria have developed mechanisms in order to avoid their destruction by antibiotics. The mechanisms are formed via biochemical pathways.[38] Bacteria may use one or more mechanism in order to survive, although some bacterial species may favour one over another.[39] There are several methods of mechanical resistance, as follows:

- *Modification of the antibiotic*: Involves the production of different enzymes which prevent the antibiotic from carrying out its function.[40]

[30] Burmeister, A. R. (2015). p. 1
[31] Von Wintersdorff, C. J. H. et al. (2016). p. 5
[32] Von Wintersdorff, C. J. H. et al. (2016). p. 5
[33] Munita, J.M. and Arias, C.A. (2016). p. 3
[34] Von Wintersdorff, C. J. H. et al. (2016). p. 3
[35] Munita, J.M. and Arias, C.A. (2016). p. 4
[36] Von Wintersdorff, C. J. H. et al. (2016). p. 3
[37] Burmeister, A. R. (2015). p. 193
[38] Munita, J.M. and Arias, C.A. (2016). p. 4
[39] Munita, J.M. and Arias, C.A. (2016). p. 4
[40] Munita, J.M. and Arias, C.A. (2016). p. 5

- *Chemical changes of the antibiotic:* Enzymes bring about chemical alterations in both gram-positive and gram-negative bacteria.[41] The enzymes catalyse reactions such as, acetylation, phosphorylation and adenylation; reducing the affinity of the drug towards its target.[42] For example, when aminoglycoside modifying enzymes (AMEs) are present they alter the hydroxyl or amino group of the aminoglycoside,[43] rendering them inactive against their target bacteria.

- *Destruction of the antibiotic:* Enzymes are produced by the bacteria, which subsequently destroy the conflicting antibiotic. For example, β-lactamase breaks the amide bond of the β-lactam ring, leading to the resistance of β-lactam antibiotics.[44] Since the production of newer generations of β-lactam antibiotics, newer enzymes capable of destroying them have simultaneously developed;[45] showing the continuous battle of antibiotic resistance faced by all involved.

- *Prevention of Access to Target:*
    - *Reduced permeability:* Gram-negative bacteria are the least permeable, due to the possession of an outer membrane.[46] The target sites of antibiotics are mostly intracellular and in particular the target sites of gram-negative bacteria are found within the cytoplasmic membrane; therefore, the antibiotic must penetrate the bacteria in order to carry out its activity.[47] Hydrophilic antibiotics such as, β-lactams and tetracyclines, penetrate the outer membrane via diffusion through channels called porins.[48] [49] Reducing the permeability of the bacteria can be accomplished by: changing the type of porins formed, altering the porin production via down-regulation or impairing the function of the porins.[50] These alterations prevent the antibiotic reaching the target site, therefore, creating a low level of antimicrobial resistance.[51]

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[41] Munita, J.M. and Arias, C.A. (2016). p. 5
[42] Munita, J.M. and Arias, C.A. (2016). p. 5
[43] Munita, J.M. and Arias, C.A. (2016). p. 5
[44] Munita, J.M. and Arias, C.A. (2016). p. 6
[45] Munita, J.M. and Arias, C.A. (2016). p. 6
[46] Blair, J. M. A. *et al.* (2014). p. 43
[47] Munita, J.M. and Arias, C.A. (2016). p. 11
[48] Blair, J. M. A. *et al.* (2014). p. 43
[49] Munita, J.M. and Arias, C.A. (2016). p. 11
[50] Munita, J.M. and Arias, C.A. (2016). p. 11
[51] Munita, J.M. and Arias, C.A. (2016). p. 11

- *Increased efflux pumps:* Efflux pumps remove antibiotics from within bacteria.[52] The pumps can either be substrate specific, for one antibiotic; or may have a broad specificity, for a number of antibiotics, these are called multidrug resistant (MDR) pumps.[53] Therefore, a high level of resistance can occur when the efflux pumps are overexpressed.[54]

- *Alterations in target sites*: Mechanisms developed through evolution, which prevent the antibiotic from reaching its target site.[55]

  - *Protection of the target:* The genes involved in this mechanism are found in the mobile genetic elements (MGEs) of bacteria.[56] Antibiotics involved in this mechanism include tetracyclines and their corresponding resistant components: Tet(M) and Tet(O).[57] Both Tet(M) and Tet(O) are found in an extensive number of bacterial species, including Streptococcus and Campylobacter.[58] The elements interact with the ribosome of the bacteria and remove the tetracycline from the target site, via a GTP-dependent process.[59] This interaction may bring about changes in the structure of the ribosome, prohibiting the antibiotic from recombining with the target site.[60]

  - *Modification of the target site:*
    - *Mutations of the target site:* Alterations in the structure of the target site prevent complete binding of the antibiotic with the site, however, it still allows the target to fulfil its usual function.[61] If a gene encoding an antibiotic target site undergoes a single point mutation, this mutation can

[52] Blair, J. M. A. *et al.* (2014). p. 43
[53] Munita, J.M. and Arias, C.A. (2016). p. 12
[54] Blair, J. M. A. *et al.* (2014). p. 43
[55] Munita, J.M. and Arias, C.A. (2016). p. 13
[56] Munita, J.M. and Arias, C.A. (2016). p. 14
[57] Munita, J.M. and Arias, C.A. (2016). p. 14
[58] Munita, J.M. and Arias, C.A. (2016). p. 14
[59] Munita, J.M. and Arias, C.A. (2016). p. 14
[60] Munita, J.M. and Arias, C.A. (2016). p. 14
[61] Blair, J. M. A. *et al.* (2014). p. 45

proliferate and bring about high levels of antibiotic resistance.[62] For example, Rifampin prevents transcription of bacteria by blocking RNA polymerase.[63] The binding site of Rifampin is found on the β-subunit of the RNA polymerase, which is encoded by the rpoB gene.[64] Resistance occurs through a single point mutation in the rpoB gene, whereby amino acid groups are replaced within the gene.[65] It leads to a reduced affinity of the Rifampin for its target but at the same time allows transcription to proceed as the normal function of the target.[66]

- *Enzymatic modification of the target site:* Enzymes cause biochemical changes to the binding site of the bacteria resulting in the insufficient binding of the antibiotic to the bacteria.[67] An example of this mechanism involves an enzyme encoded by the erm genes (erythromycin ribosomal methylation); the enzyme catalyses the methylation of the ribosome of the target organism, which leads to the resistance of macrolide antibiotics.[68]

- *Replacement or bypass of the target site:* Bacteria can develop new target sites that share similarities in their function with the former target site, however, the bacteria are not destroyed by the antibiotic.[69] The other possibility of inhibiting the action of the antibiotic, is to bypass the reactions they inhibit by overwhelming the drug with the overproduction of the target site.[70] A very important and clinically relevant example of this occurs with MRSA. The resistance of MRSA has transpired due to the gain of an external gene called mecA, which encodes Penicillin Binding Protein 2a (PBP2a).[71] The affinity of PBP2a for binding to β-lactam antibiotics is very low; such antibiotics include penicillin, which hence, cannot be used in the treatment of MRSA.[72]

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[62] Blair, J. M. A. *et al.* (2014). p. 45
[63] Munita, J.M. and Arias, C.A. (2016). p. 15
[64] Munita, J.M. and Arias, C.A. (2016). p. 15
[65] Munita, J.M. and Arias, C.A. (2016). p. 15
[66] Munita, J.M. and Arias, C.A. (2016). p. 15
[67] Munita, J.M. and Arias, C.A. (2016). p. 16
[68] Munita, J.M. and Arias, C.A. (2016). p. 16
[69] Munita, J.M. and Arias, C.A. (2016). p. 17
[70] Munita, J.M. and Arias, C.A. (2016). p. 17, 20
[71] Munita, J.M. and Arias, C.A. (2016). p. 17
[72] Munita, J.M. and Arias, C.A. (2016). p. 17

- *Resistance due to cell evolution:* Bacteria have adapted in order to survive a vast number of environmental pressures.[73] Bacteria must compete against opposing organisms for nutrients and must adapt to stresses within the host, most importantly the hosts immune system.[74] If bacteria do not adapt to their changing surroundings they can die therefore, the bacteria evolve bringing modifications that can result in antibiotic resistance. An example is the resistance of daptomycin (DAP). DAP is associated with cationic antimicrobial peptides (CAMPs) which are formed by the innate immune system, which work by modifying the cell envelope.[75] The changes are mostly electrochemical which cause the outflow of ions, and can result in the death of the organism.[76] The bacteria have developed resistance due to evolution, allowing them to resist the effects of CAMPs and protect the cell envelope.[77]

[73] Munita, J.M. and Arias, C.A. (2016). p. 21
[74] Munita, J.M. and Arias, C.A. (2016). p. 21
[75] Munita, J.M. and Arias, C.A. (2016). p. 21
[76] Munita, J.M. and Arias, C.A. (2016). p. 21-22
[77] Munita, J.M. and Arias, C.A. (2016). p. 22

4. The impact of antibiotic resistance on human health

The overuse of antibiotics in food producing animals has been a major issue for a long time which, in turn is having a major impact on human health, as well as animal health. Antibiotic resistance is influenced by both its use in veterinary and human medicine and is heightened via the transportation of animals and meat products internationally.[78] This is important as some countries protocols on the use of antibiotics in production animals or in the testing of carcases for resistant bacteria, may not be as meticulous as ours and can enhance the spread of antibiotic resistant bacteria.

The majority of bacteria that cause infections and illnesses in humans are found in food producing animals, especially within their meat, some examples of these include Salmonella, E. coli and Staphylococcus aureus.[79] Resistant bacteria can shed from the livestock into the environment, which can contaminate farmers and most importantly can contaminate workers in slaughterhouses who further transmit the bacteria to the meat products.[80] These antibiotic resistant bacteria can also spread between humans.[81] Resistant bacteria can also be transferred from the farmer to their animals, where they can proliferate, obtain further resistant genes, then transfer back to the farmer.[82] The biggest difficulty with this is that the same antibiotics being used to treat animals are also used in the treatment of human diseases. It is also possible that the use of one antibiotic, could cause resistance to several other antibiotics, which can occur when the resistant genes are linked to plasmids or transposons that are capable of being transferred to other bacteria.[83] There is also the potential threat that resistant genes from bacteria of animal origin can transfer to human bacteria, further propelling the dilemma.[84]

It is the human gastrointestinal tract that plays a role in harbouring antibiotic resistant bacteria. Many elements can alter the constitution of the flora within the human intestinal tract including, age, diet, environment and most importantly antibiotics.[85] Hence, the flora in the intestinal tract act as a reservoir for antibiotic resistant genes which can be

[78] WHO (2014). p.59
[79] Spellberg, B. et al (2016). p.4
[80] Spellberg, B. et al (2016). p.6
[81] Spellberg, B. et al (2016). p.4
[82] Officer, C. M. and Davies, D. S. (2015). p.11
[83] Rolain, J. M. (2013). p. 2
[84] WHO (2014). p.59
[85] Rolain, J. M. (2013). p.4

transported between the bacteria in the gut.[86] It has also been demonstrated via metagenomics that antibiotic resistant bacteria can be transferred from a mother to her child during birth, from her intestinal tract, or through her milk and these bacteria can remain within the child for weeks. This can be very serious as new-borns have an extremely low immunity making them more susceptible to diseases.[87]

Antibiotics are used in veterinary medicine for several reasons; for the treatment of diseases, prophylaxis and in some countries even as growth promoters.[88] The groups of antibiotics used in veterinary and human medicine are very similar causing a greater risk for the spread of resistant bacteria.[89] However, the use of antibiotics in animals, both food-producing and domesticated, more than surpasses the amount used in human medicine. The addition of antibiotics to animal's feed and water is a major factor leading to antibiotic resistance especially in the poultry and swine industries, in particular for use in prophylaxis.[90]

4.1 Fluoroquinolones

4.1.1 E. coli

One group of antibiotics with particular concern are fluoroquinolones, whom have seen a rapid rise in resistance to a number of bacteria including; Enterobacteriaceae, Salmonella and Shigella species.[91] Bacteria such as E. coli, are naturally present in the gastrointestinal tract of both humans and animals however, can cause severe infections in humans. These can include urinary tract infections, blood stream infections, peritonitis, skin infections and even meningitis in new-born babies.[92] The main issue regarding this is that some of the strains causing these diseases can be transmitted via the food chain to humans.[93] An examination was carried out in the United Kingdom where isolates of E. coli were collected from broilers and turkeys and tested for resistance to several antibiotics important in human medicine.[94] It was observed that 25% of the strains sampled from the

[86] Rolain, J. M. (2013). p.6
[87] Rolain, J. M. (2013). p.6
[88] WHO (2014). p.59
[89] WHO (2014). p.59
[90] Spellberg, B. et al (2016). p.7
[91] Spellberg, B. et al (2016). p.6
[92] WHO (2014). p.12
[93] WHO (2014). p.12
[94] Grace, K. et al. (2014). p.38

broilers and 17% of the strains from turkeys were resistant to Ciprofloxacin.[95] The resistance of E. coli to fluoroquinolones has developed due to mutations and has shown the largest amount of resistance to them, in comparison with other antibiotics.[96]

4.1.2 Salmonella

Salmonella are zoonotic bacteria and are the prime causative agents of foodborne diseases, spread mainly via the intake of animal products such as, raw or undercooked meat.[97] Salmonella is usually found in the intestinal tract of food-producing animals and so have the potential to contaminate carcases in slaughterhouses. Salmonella is a major public health concern and causes problems such as gastritis, which is mostly self-limiting.[98] However, strains such as Salmonella enterica serotype Typhimurium can cause serious and invasive infections which can be potentially life-threatening due to the resistance of the bacteria to a number of antibiotics.[99] The antibiotic resistant determinants carried by this strain in its genome can be transferred to other serotypes, but can also obtain further resistant elements.[100] The same study that was carried out in the UK for E. coli, was also carried out with Salmonella and it was found that 6 of the Salmonella strains were resistant to Ciprofloxacin, causing a significant problem for the treatment of these illnesses.[101]

4.1.3 Shigella

Shigella species cause diarrhoeal diseases and dysentery mainly in poor and overcrowded conditions.[102] It is obtained via the consumption of contaminated food and water or via direct contact with an infected person.[103] The majority of people convalesce however, Shigellosis has the ability to be particularly fatal in young children, below 5 years of age.[104] Therefore, the treatment of Shigella species is a major concern especially in developing countries and due to the resistance of the bacteria to a number of antibiotics.

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[95] Grace, K. et al. (2014). p.38
[96] WHO (2014). p.12
[97] WHO (2014). p.23
[98] WHO (2014). p.25
[99] WHO (2014). p.23
[100] WHO (2014). p.24
[101] Grace, K. et al. (2014). p.40
[102] WHO (2014). p.25
[103] WHO (2014). p.25
[104] WHO (2014). p.25

Fluoroquinolone's are routinely used in veterinary medicine, and so, it is highly important that their use is sufficiently managed in order to effectively treat human conditions caused by these bacteria.[105] Fluoroquinolones are one of the few existing treatments for critical Salmonella and E. coli infections and therefore, should be reserved only for extreme cases in veterinary medicine.[106]

4.2 Methicillin Resistant Staphylococcus aureus (MRSA)

Methicillin Resistant Staphylococcus Aureus (MRSA), is another major health concern that has had a lot of exposure within recent years. MRSA first emerged in the 1960s and is now one of the most important concerns in public health.[107] MRSA causes extremely serious infections of the blood stream, bones and skin, particularly potent in post-surgical wound infections and has also brought about a significant increase in mortality rates.[108] It is caused by multi-resistant strains of S. aureus that are complex to treat.[109] These strains have the mecA gene that encodes a penicillin binding protein, allowing them resistance to these antibiotics.[110] Methicillin resistant coagulase negative staphylococci (MRCoNS) are understood to be the source of the mecA gene, which is capable of being transferred to S. aureus; the most pathogenic of the staphylococci.[111] Animal products such as meat, have been found to be a source of MRCoNS, discovered via a study in Europe that detected several species of MRCoNS in minced meat.[112] The major problem with the resistance of these strains is in the requirement to utilise second-line antibiotics.[113] The biggest issue with second-line medicines is not only their expense, but also their critical side-effects that require more intensive monitoring of patients.[114] This in turn leads to more expensive health care and also places an increased pressure on the health system, that is already struggling.

[105] WHO AGISAR (2011). p.3
[106] WHO AGISAR (2011). p.31
[107] WHO (2014). p.19
[108] WHO (2014). p.19
[109] WHO (2014). p.19
[110] WHO (2014). p.19
[111] Bhargava, K. and Zhang, Y. (2014). p.56
[112] Bhargava, K. and Zhang, Y. (2014). p.56-57
[113] WHO (2014). p.21
[114] WHO (2014). p.21

4.3 Cephalosporins

4.3.1 Klebsiella

Another group of antibiotics that are at risk are 3rd and 4th generation Cephalosporins. Bacteria with a risk to developing resistance to these antibiotics include Klebsiella pneumoniae. Klebsiella pneumoniae is a dangerous bacteria for immunocompromised individuals such as new-borns or terminally ill patients.[115] It can cause urinary tract infections, respiratory infections, infections of the bloodstream and can cause mortality rates above 50% even with treatment.[116] Similarly to Salmonella, Klebsiella can obtain antibiotic resistance through the transfer of mobile genetic elements.[117] The biggest issue with Klebsiella is that it has natural resistance to penicillin's such as, Amoxicillin and also has resistance to fluoroquinolones and trimethoprim-sulphonamide, leaving limited options for the treatment of the bacteria.[118] The most utilised treatment for K. pneumoniae is 3rd generation cephalosporins; the ongoing use has led to the development of resistance toward these bacteria.[119] The substantial resistance of these bacteria for a vast number of antibiotic groups, poses a considerable threat to the well-being of humans and deteriorates the advancement of human medicine.

4.3.2 Streptococcus

Streptococcus pneumoniae is the leading cause of pneumonia which can be fatal especially to young children, as well as causing acute otitis media and the more severe meningitis.[120] S. pneumoniae developed resistance to penicillin and other beta-lactam antibiotics via mutations in the genes coding the penicillin binding proteins (PBPs), which are located within the bacterial cell wall.[121] This causes massive repercussions for human medicine, as penicillin has always been an important antibiotic in treating life-threatening infections caused by such bacteria, and it has substantially reduced fatality rates, which, depending

[115] WHO (2014). p.15
[116] WHO (2014). p.15
[117] WHO (2014). p.15
[118] WHO (2014). p.15
[119] WHO (2014). p.16
[120] WHO (2014). p.21
[121] WHO (2014). p.21

on the infection could be up to 90%.[122] Therefore, resistance to such antibiotics will cause grave outcomes in the future in particularly for patients with meningitis.

The consequences forthcoming due to antibiotic resistance are a major concern to public health and will show countless implications in human medicine particularly in the treatment of fatal diseases for years to come. Antibiotics are important for modern medicine therefore antibiotic resistance will prevent the advancement of medicine and may even regress the advances that have been made to date. In the long-run the overuse of antibiotics in food producing animals will eventually lead to treatment failure for life-threatening illnesses and infections. This failure will result in increased fatality rates from illnesses that would have been successfully treatable with antibiotics previously. Therefore, increased realisation that immediate action is required to avoid the improper use of antibiotics within the food production industry.[123]

[122] WHO (2014). p.23
[123] WHO (2014). p.59

5. Alternatives to Antibiotics

In order to reduce antibiotic use, antibiotics may be replaced with alternative remedies. There are some remedies that have proven to be effective in reducing the effects of bacteria and should be promoted more in order to reduce antibiotic resistance of bacteria. Substitutes include:

1. *Plant Derived Antimicrobials:* An experiment was carried out checking the antibiofilm ability of plant derived antimicrobials on the biofilm of Listeria monocytogenes.[124] Biofilms can form on equipment and allows the bacteria to survive the food processing for long durations allowing continuous contamination of food.[125] The biofilm protects the bacteria from disinfectants, desiccation and antimicrobials.[126] The FDA has classed the following plant derived antimicrobials as safe for use and were tested during this experiment; Trans-cinnamaldehyde from cinnamon bark, Carvacrol and Thymol from oregano oil and Eugenol from cloves.[127] The results yielded showed a decrease in the biofilm formation and even inactivated some pre-formed biofilms on a number equipment surfaces.[128]

2. *Bacteriophages:* These are viruses found in natural habitats with the capability of inserting themselves within bacteria, in order to maintain microbial balance.[129] Bacteriophages are much better alternatives to antibiotics due to their many advantages. Bacteriophages are specific to their host and therefore, don't cause dysbacteriosis and other side effects unlike antibiotics.[130] There is no risk to the host due to the fact that they target bacterial cells and not the hosts cells.[131] The formation of bacteriophages is fast and relatively inexpensive compared to antibiotics which can cost millions and can take years to produce.[132] Resistance is less concerning here due to the fact a number of bacteriophages can have the same target and also mutations allow the bacteriophages to evolve with their target host,

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[124] Upadhyay, A. *et al.* (2013). p.79
[125] Upadhyay, A. *et al.* (2013). p.79
[126] Upadhyay, A. *et al.* (2013). p.79
[127] Upadhyay, A. *et al.* (2013). p.79
[128] Upadhyay, A. *et al.* (2013). p.82
[129] El-shibiny, A. and El-sahhar, S. (2017). p.2
[130] El-shibiny, A. and El-sahhar, S. (2017). p.5
[131] El-shibiny, A. and El-sahhar, S. (2017). p.5
[132] El-shibiny, A. and El-sahhar, S. (2017). p.5

which prevents acquired resistance from developing.[133] Bacteriophages only replicate when their target is present whereas, antibiotics may be metabolised and excreted without having reached their target.[134] Bacteriophages are so small they are capable of penetrating areas of the body that antibiotics cannot, such as, the blood brain barrier.[135]

3. *Probiotics:* Probiotics are known to have many health benefits to both humans and animals alike. Probiotics can be used as an alternative to antibiotics but must be screened before they are approved for use in livestock, due to the fact that they are capable of carrying and transferring antibiotic resistant genes via horizontal gene transfer.[136] Studies in this area have shown that probiotics can reduce antibiotic use by inhibiting diseases and enhancing growth in food-producing animals.[137] Probiotics improve the microflora of livestock which is crucial to produce 70% of the acquired energy of ruminants and 30% in monogastric animals.[138] The benefits of probiotics have been shown in both poultry and aquaculture industries.[139] However, little success was found in cattle and sheep except for reducing the shedding of the E. coli strain 0157:H7, a food-borne bacteria capable of causing illness in humans.[140]

It is important that producers become more open to the use of substitutes for antibiotics, in order to reduce resistance and to protect the future of their livestock.

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[133] El-shibiny, A. and El-sahhar, S. (2017). p.5
[134] El-shibiny, A. and El-sahhar, S. (2017). p.5
[135] El-shibiny, A. and El-sahhar, S. (2017). p.6
[136] Imperial, I. C. V. J. and Ibana, J. A. (2016). p.1
[137] Imperial, I. C. V. J. and Ibana, J. A. (2016). p.4
[138] Imperial, I. C. V. J. and Ibana, J. A. (2016). p.4
[139] Imperial, I. C. V. J. and Ibana, J. A. (2016). p.4-5
[140] Imperial, I. C. V. J. and Ibana, J. A. (2016). p.4

6. Antibiotic use and strategies to combat resistance in countries worldwide

It is important to study the way in which different countries allow antibiotics to be used because of the increasing concern for antibiotic resistance and due to the increase in international trade being conducted between countries. The trade of products of animal origin have aided in the spread of bacteria and therefore in the spread of antibiotic resistance globally.[141] Countries that are of particular concern are the major exporting countries like the United States of America for example.[142] These countries have the highest threat for resistance due to the high demand on production to produce a higher output for exportation.[143] We will now look at the usage of antibiotics in different countries and also the strategies these countries have to reduce antibiotic resistance.

Here, I will compare the use of antibiotics in different countries around the world and also the strategies that the governmental bodies and agencies are attempting to implement within their country. I will also discuss the success, if any, the countries have had in the implementation of these changes to prevent any further resistance to critical, life-saving antibiotics.

6.1 United States

6.1.1 Antibiotic use

Antibiotics have been used in food producing animals in the United States since the 1950s.[144] The use of antibiotics in the United States is governed by the department of health and human services' food and drug administration (FDA). The FDA protects human health by ensuring the proper use of human and veterinary drugs at the same time safeguarding the countries food products.[145] Working together with the FDA are other governmental agencies, the U.S. department of agriculture (USDA) and the centres for disease control (CDC), which carry out other activities including surveillance, investigations and analysing.[146]

[141] Wall, B. A. et al. (2016). p.33
[142] Wall, B. A. et al. (2016). p.33
[143] Wall, B. A. et al. (2016). p.33
[144] AUPA (2010). p.1
[145] FDA (2017)
[146] Christie, S. (2010)

In order for the legal use of antibiotics in food-producing animals, they have to be permitted for use in these animals by the food and drug administration (FDA).[147] In the United States the use of antibiotics in food-producing animals are regulated on the ground and prescribed for use by veterinarians to be utilised in particular situations:[148]

1. Therapeutic treatment of an animal based on the diagnosis by a qualified veterinarian.[149]
2. Antibiotics are given to control a disease outbreak on a farm and to prevent it spreading to other animals.[150]
3. Antibiotics are used for prophylaxis during high risk times of the year.[151] Prophylaxis can be done at either therapeutic or sub-therapeutic doses, and has a longer administration period than with treatment.[152] Prophylaxis is carried out as livestock are raised in intense environments which supports the spread of diseases.[153] These environments allow nose to nose contact between animals hence, veterinarians suggest the use of antibiotics as a preventative to diseases.[154] The most common administration method for prophylaxis is via the food or water especially in swine and poultry production.[155] The idea behind prophylaxis is that the animals will require less antibiotics in the long run.[156]
4. In the United States antibiotics were, until recently, approved to be used as growth promoters (GPs) and to increase the food conversion ratio (FCR).[157] Antibiotics can kill bacteria in the gastrointestinal tract allowing better conversion of feed to muscle mass providing a faster development and therefore, a higher production output.[158] Since January this year, the FDA decided that the use of antibiotics as

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[147] AUPA (2010). p.2
[148] AMI (2015)
[149] AMI (2015)
[150] AMI (2015)
[151] AUPA (2010). p.1
[152] AUPA (2010). p.2
[153] AUPA (2010). p.1
[154] AMI (2015)
[155] AUPA (2010). p.2s
[156] AMI (2015)
[157] AUPA (2010). p.1
[158] AMI (2015)

growth promoters will not be permitted any longer.[159] The strategy to phase out the undesirable use of antibiotics is outlined in the Guidance for Industry #213.[160]

6.1.2 Strategies to combat antibiotic resistance

The U.S. food and drug administration is responsible for encouraging the cautious utilisation of critically important antibiotic medicines in food-producing animals.[161] The aim of their strategies is to work with the food-production sector in order to safeguard the health and well-being of humans.[162] The FDA are implementing their strategies by publicising two documents as a guidance to aid in the phase out of the use of antibiotics in food producing animals for growth promoters etc. and to ensure the medicinal use of antibiotics under the supervision of veterinarians.[163]

The antibiotic medicines being aimed at here by the FDA include:

- Medicines important for the treatment of human conditions both mild and life-threatening.[164]
- Existing FDA-approved medicines to be used as growth promoters and to increase the feed conversion ratio.[165]
- Over-the-counter medicines.[166]
- Antibiotics for use in feed or water.[167]

According to the FDA, in 2012 an estimated 14.6 million kilograms of antibiotics were sold for use in food-producing animals, which is four times the amount sold for use in human medicine.[168] In 2012, the FDA's Centre for Veterinary Medicine released a document called 'The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals,' Guidance for Industry (GFI) #209. This document sets out the importance of the cautious use of antibiotics, in other words preventing their inappropriate and unnecessary use, due to their contribution in the development of antibiotic resistant

[159] FDA, Centre for Veterinary Medicine (2017)
[160] FDA, Centre for Veterinary Medicine (2017)
[161] FDA (2017)
[162] FDA (2017)
[163] FDA (2017)
[164] FDA (2017)
[165] FDA (2017)
[166] FDA (2017)
[167] FDA (2017)
[168] Teillant, A. and Laxminarayan, R. (2015). p.1

bacteria.[169] The document centres on the use of medicinally critical antibiotics and restricting their use in food-producing animals, with the consultation of licensed veterinarians.[170] In the document the FDA recommends taking a proactive style in their strategies, to ensure the use of antibiotics is always essential and appropriate.[171]

The other document publicised by the FDA in 2013 is called, 'New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions,' Guidance for industry #213. This document is to be used in conjunction with the GFI #209. This document is designed to be a guidance, particularly for pharmaceutical companies to adjust the labelling on their products.[172] The overall aim is to remove from the packaging the use of antibiotics for production purpose's, meaning to prevent their use for growth promotion and to increase the feed conversion ratio.[173] They are also encouraged to include, where possible, scientific information for the basis of treatment, control and prophylaxis.[174] They also recommend that antibiotics used in feed and water should no longer be sold over the counter but via prescription basis only from a licensed veterinarian.[175]

Many of the growth promoters administered to food-producing animals in the U.S. were classed as life-saving in human medicine by the World Health Organisation (WHO).[176] After a report carried out in 2013, by the CDC, which voiced distress for the use of antibiotics as growth promoters in food-producing animals, the FDA decided action was necessary, bringing about the formation of the GFI #213.[177]

The importance of veterinary compliance in implementing these strategies is immeasurable. The knowledge and clinical training of a veterinarian is the crucial component for the strategy to work.[178] As part of the strategy, it is required that antibiotics are used appropriately and when necessary. Therefore, the veterinarian must ensure that when diagnosing a disease in an animal or herd, the exact bacteria must be identified, so

[169] FDA (2012). p.3
[170] FDA (2012). p.3
[171] FDA (2012). p.20
[172] FDA (2017)
[173] FDA (2017)
[174] FDA (2017)
[175] FDA (2017)
[176] AUPA (2010). p.1
[177] AMI (2015)
[178] FDA (2017)

the correct antibiotic or combination of antibiotics can be prescribed, for a given period.[179] New medicines manufactured for animals are labelled as either; over-the-counter (OTC), veterinary prescription (Rx) or veterinary feed directive (VFD).[180] Directions for use of over-the-counter products can be provided by a lay person and not by a veterinarian.[181] However, the other forms of medicines require directions to be provided by a licensed veterinarian, giving information about the proper usage and purpose intended for the antibiotic prescribed.[182] This is one of the main areas the FDA wishes to modify, so that over-the-counter products will require a prescription and therefore, the use will be supervised by a licensed veterinarian, reducing the unnecessary use of the product.[183]

When preventing a disease, there are important elements to be considered by a veterinarian when practicing cautiously.[184] The veterinarian must decide if the antibiotic is suitable for prophylaxis if; the medicine will be successful against an illness and the causing bacteria, its use against the illness is considered to be a recognised veterinary practice and there are no other options available.[185]

The problem with the FDA's documents is that they are only designed to be a guidance for the companies and other parties involved. It states in the documents that "It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statues and regulations." (FDA, 2013). The FDA feels that the most successful approach to achieving their goals is to offer this voluntary style guidance, allowing the parties and pharmaceutical companies to reach the targets at their own pace, with the hope of them being more compliant.[186] The FDA's guides also provide information to companies in order to assist and accelerate the voluntary course.[187] It is also required that when the companies intend to comply and make changes, that they notify the FDA of their activities in order for the FDA to formulate their reports.[188]

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[179] FDA (2017)
[180] FDA (2013). p.4
[181] FDA (2013). p.4
[182] FDA (2013). p.4
[183] FDA (2017)
[184] FDA (2017)
[185] FDA (2017)
[186] FDA (2013). p.5
[187] FDA (2013). p.6
[188] FDA (2013). p.6

However, even though the guidelines for both of the GFI #209 and GFI #213 are voluntary the question we have is how will the government ensure people will comply and not continue using the antibiotics in the prohibited way? When the labelling is replaced, anyone using the medicines in an inappropriate or unnecessary manner will be violating the Federal Food, Drug and Cosmetic act.[189] The problem with this is that due to the voluntary nature of the FDA’s strategy, it is only a violation when the pharmaceutical companies voluntarily decide to change the labels on their products, otherwise the user isn’t doing anything wrong. The FDA has been consulting with the American Veterinary Medical Association and other animal production organisations, they have listened to the apprehensions of producers and veterinarians via outreach programs and are confident that they will all comply.[190]

In 2016, the FDA released a report on the sales and distribution of antibiotics in food-producing animals for the year 2015. The report shows an increase by 1% in sales and distribution from 2014 to 2015 continuing the upward trend of antibiotic use.[191] However, this 1% increase is the lowest increase since 2009, where an increase of 24% has been seen from 2009 to 2015.[192] The sales and distribution of antibiotics critical in human medicine rose by 2% from 2014 to 2015.[193] Tetracyclines sold the highest volume, increasing by 4%.[194] Lincosamides actually saw a decline in sales by 22% from 2014 to 2015.[195] The proportion of critical antibiotics sold over-the-counter for use in production animals has decreased from 98% to 97% between 2009 to 2015.[196] Therefore, according to this report the use of vital antibiotics in food-producing animals is continuing to rise, with the implementation of the FDA’s strategy, you would expect the sales to have decreased however, they have not and it’s still an immense concern.

[189] FDA (2017)
[190] FDA (2017)
[191] FDA (2016). p.6
[192] FDA (2016). p.6
[193] FDA (2016). p.6
[194] FDA (2016). p.6
[195] FDA (2016). p.6
[196] FDA (2016). p.6

6.2 Australia

6.2.1 Antibiotic use

The Australian government is leading the way in antibiotic use in food-producing animals. There are three main uses of antibiotics in Australia, most commonly in intensively farmed cattle, pigs and poultry:[197]

1. Antibiotics are used for therapeutic use for the treatment of illnesses in individual animals within a herd.[198]

2. Antibiotics may be used for prophylaxis in healthy animals under the supervision of a licensed veterinarian.[199] It can be used for prevention against life-threatening illnesses or diseases that threaten production.[200]
3. Antibiotics may also be used in sub-therapeutic doses as growth promoters, to improve the feed conversion ratio or to control diseases caused by protozoa for example, Coccidia.[201] These can be used without veterinary supervision and the antibiotics are not critical to human medicine.[202]

6.2.2 Strategies to combat antibiotic resistance

In 2013, the Australian Antimicrobial Resistance Prevention and Containment (AMRPC) steering group was formed. It is composed of the Department of health and the Department of agriculture and also includes, as its members, the chief medical officer and the chief veterinary officer.[203] The group governs and controls the antibiotic resistance prevention and strategy for Australia.[204] The Australian government are also consulting with other international bodies such as the World Health Organisation (WHO), to ensure international targets and strategies for antibiotic resistance are being met.[205] They are also assisting the WHO in the formation of a Global Action Plan (GAP) for antibiotic resistance.[206] The Australian government also works with the world organisation for animal health (OIE),

[197] JETACAR (1999). p.16
[198] Shaban, R. Z. et al. (2014). p.43
[199] Shaban, R. Z. et al. (2014). p.43
[200] JETACAR (1999). p.16
[201] JETACAR (1999). p.16
[202] Shaban, R. Z. et al. (2014). p.43
[203] Shaban, R. Z. et al. (2014). p.43
[204] Shaban, R. Z. et al. (2014). p.43
[205] DOH (2016)
[206] DOH (2016)

with whom they have worked with to form protocols for the use of antibiotics in food-producing animals.[207]

The strategy of the Australian government consists of seven objectives, that are intended to be achieved between 2015 to 2019:

- The first objective, is to boost the recognition and increase the knowledge of the public about antibiotic resistance by educating and training people about the repercussions the overuse of antibiotics will bring in the future.[208] Since 2012, Australia has supported the international programme, Antibiotic Awareness Week in order to educate the public on the appropriate use of antibiotics in both human and veterinary medicine.[209]
- The second objective, involves applying efficient antibiotic stewardship practices in both human and veterinary medicine, to ensure that antibiotics are being prescribed and administered in a cautious and necessary manner.[210] It's important to ensure that veterinarians are prescribing antibiotics appropriately when the correct bacteria has been detected.[211]
- Objective three, is to develop a well-structured surveillance programme to assess, analyse and report on antibiotic use and resistance.[212] A global harmonised surveillance programme is vital in order to fully comprehend the consequences of antibiotic resistance and to identify developing resistance and movements, to enable governments to form mutual policies and objectives.[213]
- The fourth objective is to develop prevention and control measures in both veterinary and human medicine.[214] An improvement in hygiene and better husbandry will prevent diseases and help reduce the spread of resistant bacteria.[215] Some options they recommend include, protective apparatus such as gloves, thorough cleaning with disinfection and also preventative measures of diseases such as vaccines.[216]

[207] Murray, G. (2001). p.86
[208] Australian Department of Health and Department of Agriculture (2015). p.8
[209] Australian Department of Health and Department of Agriculture (2015). p.9
[210] Australian Department of Health and Department of Agriculture (2015). p.11
[211] Australian Department of Health and Department of Agriculture (2015). p.13
[212] Australian Department of Health and Department of Agriculture (2015). p.16
[213] Australian Department of Health and Department of Agriculture (2015). p.16
[214] Australian Department of Health and Department of Agriculture (2015). p.20
[215] Australian Department of Health and Department of Agriculture (2015). p.20
[216] Australian Department of Health and Department of Agriculture (2015). p.20

- Objective five, is designed to incorporate all of the necessary bodies in order to encourage the study and investment for evolving new products and methods to prevent and supress antibiotic resistance.[217]
- Objective six notices that there is a rise in international trade and an increase in people emigrating to different countries.[218] Therefore, it is a global interest that countries intensify their forces to battle the issue of antibiotic resistance.[219] Australia intend to do this by working with other international bodies such as WHO, OIE and the food and agriculture organisation (FAO).[220]
- The seventh objective, observes that the achievement of these seven objectives requires communication between a number of bodies including, the government, the Australian Veterinary Association, animal producers, agricultural and pharmaceutical producers, as well as other international bodies.[221] Clear consultation between all of the parties involved would allow the defeat against antibiotic resistance.[222]

A progress report was due to be issued by the Australian government this year in October 2017, however it has not yet been released. The most recent report released by the government contained an analysis of the sales from 2005 to 2010. In Australia, the antibiotics that are approved for use in food-producing animals are schedule 4 medicines, which are prescription only.[223] Exceptions to these are tylosin and coccidiostats, which are not human medicines.[224] The report does not show much of a reduction in sales from 2005 to 2010, this maybe be due to poor surveillance and reporting during some of the period.[225] The total sales on antibiotics decreased slightly from 645.1 tons in 2005 to 625.2 tons in 2010.[226] It was shown that 98% of the antibiotics sold were intended for use in food-producing animals.[227] However, the report also demonstrates the breakdown of the use of

[217] Australian Department of Health and Department of Agriculture (2015). p.24
[218] Australian Department of Health and Department of Agriculture (2015). p.27
[219] Australian Department of Health and Department of Agriculture (2015). p.27
[220] Australian Department of Health and Department of Agriculture (2015). p.27
[221] Murray, G. (2001). p.86
[222] Australian Department of Health and Department of Agriculture (2015). p.30
[223] Australian Pesticides and Veterinary Medicine Authority (2014). p.14
[224] Australian Pesticides and Veterinary Medicine Authority (2014). p.14
[225] Australian Pesticides and Veterinary Medicine Authority (2014). p.20
[226] Australian Pesticides and Veterinary Medicine Authority (2014). p.20
[227] Australian Pesticides and Veterinary Medicine Authority (2014). p.20

the antibiotics in food-producing animals which were as follows; 43% for therapeutic use, 6% for growth promoters and 51% for use as coccidiostats.[228]

The highest use of antibiotics was found in the poultry industry and was also found to have increased from 385 tons to 406.4 tons from 2005 to 2010. Use in cattle and sheep was much lower and was found to have decreased from 163.8 tons to 133.3 tons and use in the porcine industry was lower again showing a decline from 106.1 tons to 104.2 tons.[229]

In 2003, the Expert Advisory Group on Antimicrobial Resistance (EAGAR) composed a report on the importance of groups of antibiotics.[230] Cephalosporins are rated medium/high importance in human medicine. The most commonly used cephalosporin in food-producing animals is Ceftiofur, a third-generation cephalosporin, who's use has increased from 2005 to 2010.[231] Any fluoroquinolone rated as high importance in human medicine i not allowed to be used in food-producing animals and where a fluoroquinolone is permitted for use in veterinary medicine, it is only allowed to be used in non-food animals.[232]

Due to the fact there has been reductions in antibiotic use in Australia since 2005 and that the Australian government had already set up the EAGAR group in 2003, their strategy has been progressing and will expectantly continue to do so.

[228] Australian Pesticides and Veterinary Medicine Authority (2014). p.20
[229] Australian Pesticides and Veterinary Medicine Authority (2014). p.21
[230] Australian Pesticides and Veterinary Medicine Authority (2014). p.50
[231] Australian Pesticides and Veterinary Medicine Authority (2014). p.53
[232] Australian Pesticides and Veterinary Medicine Authority (2014). p.53

6.3 Europe

6.3.1 Antibiotic use

The use of antibiotics in Europe is slightly different compared to other countries around the world. However, they share some of the same uses; antibiotics may be used to treat a disease in an individual animal, at a therapeutic dose, for a short duration of time.[233] Antibiotics may also be used for prophylaxis, administered in sub-therapeutic doses via the feed or water supply for a long duration of time.[234]

Since January 1st 2006, a new feed additives regulation 1831/2003/EC on additives for use in animal nutrition came into place and replaced the Directive 70/524/EEC on additives in feeding-stuffs.[235] This new regulation places a ban on the use of antibiotics as a feed additive with the intended use as a growth promoter to increase the feed conversion ratio.[236] The initial restriction on using antibiotics as growth promoters was first requested by the British government in 1969, when they set up the Swann committee.[237] The Swann committee was established after the detection that resistance to oxytetracycline could be transferred from livestock to Salmonella enterica serovar Typhmurium.[238] These findings brought about the ban of penicillin, streptomycin and tetracyclines for use as growth promoters.[239]

The Swedish government began investigations into antibiotic resistance in the 1980s, leading to Sweden being the first country in Europe to ban the use of growth promoters in food-producing animals in 1986.[240] In Denmark, in 1995, they created a programme called the DANMAP, which observed the antibiotic resistance in livestock and how the inhibition of growth promoters impacted the herds health.[241] The results yielded were highly successful which led to the complete ban on growth promoters in Denmark by 2000.[242] In 1999, the European Union banned the use of growth promoters from antibiotic

[233] Compassion in world farming (2011). p.8
[234] Compassion in world farming (2011). p.8
[235] European Union (2005). p.1
[236] European Union (2005). p.1
[237] Cogliani, C. et al (2011). p.274
[238] Cogliani, C. et al (2011). p.274
[239] Cogliani, C. et al (2011). p.274
[240] Cogliani, C. et al (2011). p.274
[241] Cogliani, C. et al (2011). p.276
[242] Cogliani, C. et al (2011). p.276

groups used to treat human diseases, including Tylosin and all the other antibiotics were then prohibited for use in 2006.[243]

6.3.2 *Strategies to combat antibiotic resistance*

The European commission launched an action plan to combat antibiotic resistance. The action plan is based on three main objectives:

1. The first objective is to implement best practice throughout all the member states.[244] This involves improving surveillance and reports on the use and resistance of antibiotics, with the use of evidence and data collection.[245] It's also essential to improve communication between the member states in order to reach the same objectives.[246] This will be done by providing current and up-to-date information for the member states to maintain education at a high in order to encourage them to continue their efforts.[247] A major factor in best practice is to ensure the highest degree of preventative and control measures are in place.[248] These measures include biosecurity, improving animal husbandry, hygiene and vaccination.[249]
2. An important objective is to promote better research and development in order to discover new technologies, methods and other possibilities for the treatment and prevention of illnesses in farm-producing animals.[250] Improving diagnostics is also vital in order to detect the exact causative agent and deciding whether or not antibiotic treatment is appropriate and necessary.[251] In order to incorporate the backing of all member states the European Commission are offering incentives for members to carry-out research and development and to consider recommendations for improvement.[252]
3. The final objective of the European Commission is to solve the issue on a global level.[253] That is to work side by side with other bodies such as the WHO, OIE and

[243] Cogliani, C. et al (2011). p.275
[244] European Commission (2017). p.6
[245] European Commission (2017). p.7
[246] European Commission (2017). p.8
[247] European Commission (2017). p.9
[248] European Commission (2017). p.10
[249] European Commission (2017). p.10
[250] European Commission (2017). p.13-14
[251] European Commission (2017). p.15
[252] European Commission (2017). p.16
[253] European Commission (2017). p.18

FAO.[254] The European Commission contributes to the work of these bodies including the Global Action Plan (GAP) supervised by WHO and is also involved in the work of the G7 and G20 forums.[255] Working on a global level also involves helping developing countries by contributing to research and development, providing these countries with programmes to improve their health systems and reduce their antibiotic resistance.[256]

The success on the implementation of the strategies from the European Commission will be discussed on country basis and how successful they have been at implementing them as individual governments.

6.3.3 Progress in Denmark

In 1995, Denmark formed the Danish Antimicrobial Resistance Monitoring and Research Programme (DANMAP), a surveillance and monitoring programme for antibiotic resistance in food-producing animals and the effect that the prevention of growth promoter has had on production.[257] DANMAP has a number of aims in order to tackle antibiotic resistance including:

- To observe antibiotic use in veterinary and human medicine.[258]
- To inspect the incidence of antibiotic resistance in bacteria sampled from production animals, humans, meat and other foods of animal origin.[259]
- To examine the correspondence between antibiotic use and resistance.[260]
- To detect the ways in which resistance spreads and additional research.[261]

The decrease in antibiotic use after 1994 was due to limiting veterinary profits from medicine sales and implementing better preventative approaches with constant veterinary calls.[262] Another factor, the implementation of the cascade rule, was particularly successful

[254] European Commission (2017). p.18
[255] European Commission (2017). p.18
[256] European Commission (2017). p.20
[257] Cogliani, C. et al (2011). p.276
[258] Bager, F. et al (2016). p.10
[259] Bager, F. et al (2016). p.10
[260] Bager, F. et al (2016). p.10
[261] Bager, F. et al (2016). p.10
[262] Bager, F. et al (2016). p.16

in reducing the use of tetracyclines.[263] In 2002, fluoroquinolone use was restricted in food producing animals.[264] In 2010, a voluntary ban on cephalosporin use in the porcine industry was enforced, and later the dairy cattle industry adopted the same idea.[265] Between 2010 and 2011, a yellow card scheme was established which launched threshold levels for antibiotic use in pigs and if any producers go over this threshold per pig, legal action will be brought against them.[266] In 2000, the Danish Veterinary and Food Administration (DVFA) began collecting data on all prescribed medicines for use in animals, including growth promoters and coccidiostatic agents.[267]

The data collected by the DVFA showed that the overall use of antibiotics in 2016 reduced by 5% from 2015.[268] The use in per industry is as follows; pigs: 75%, cattle: 12%, fur animals: 5% and poultry: 2%.[269] In 2016, a 4% reduction was found in the porcine industry from 2015, this is important as pigs are the main influencer of antibiotic use in Denmark.[270] However, the use of colistin in porcine increased in 2016 by 40kg, which is of concern to the Danish government.[271] Some of the fluctuations seen in antibiotic use in porcine is due to outbreaks of infections caused by Lawsonia intracellularis and porcine multi-systemic wasting disease (PMWS), however, the industry is still improving.[272]

The poultry industry, 2 years previous to this report, has seen a number of severe disease outbreaks.[273] However, in 2016 the use of antibiotics reduced back to the level previous to these outbreaks.[274] In the aquaculture industry, the lowest recorded antibiotic use in 10 years was found.[275]

The overall utilisation of antibiotics was decreased by 49% from 1994 to 2016.[276] The main explanation for the reduction was due to the discontinued use of growth

[263] Bager, F. et al (2016). p.16
[264] Bager, F. et al (2016). p.16
[265] Bager, F. et al (2016). p.16
[266] Bager, F. et al (2016). p.17
[267] Bager, F. et al (2016). p.17
[268] Bager, F. et al (2016). p.16
[269] Bager, F. et al (2016). p.19
[270] Bager, F. et al (2016). p.16
[271] Bager, F. et al (2016). p.16
[272] Cogliani, C. et al (2011). p.276
[273] Bager, F. et al (2016). p.16
[274] Bager, F. et al (2016). p.16
[275] Bager, F. et al (2016). p.16
[276] Bager, F. et al (2016). p.19

promoters between 1994 and 1999.[277] However, the use of critical antibiotics has stayed low for 2016.[278]

6.3.4 Progress in the United Kingdom

The majority of animal producers in the United Kingdom (UK) ceased the use of antibiotic growth promoters previous to the EU ban in 2006.[279] However, when the UK initially banned antibiotics they did not supply sufficient means to create a monitoring system.[280] When the ban was implemented the British government supplied assistance via reports composed by the Danish government and the WHO.[281] Pharmaceutical corporations also provided information to animal producers of alternate methods to be used to replace the use of growth promoters.[282]

In 2014, the UK commenced the statutory EU coordinated monitoring system.[283] To begin with the data was collected on a voluntary basis but became compulsory and is specified in the UK Veterinary Medicines Regulations.[284] However, the data they collect does not incorporate wastage and international trade.[285] The results of the monitoring are represented in the Veterinary antibiotic resistance and Sales Surveillance (VARSS) report.[286]

The sales are represented as a theoretical unit called the Population Correction Unit (PCU).[287] The PCU incorporates the number of animals and the weight of the animals during treatment.[288] The amount of antibiotics sold are represented as mg/PCU which is equal to mg/kg of animals.[289] Therefore, one PCU is equal to one kilogram of animal

[277] Bager, F. et al (2016). p.19
[278] Bager, F. et al (2016). p.16
[279] Cogliani, C. et al (2011). p.277
[280] Cogliani, C. et al (2011). p.275
[281] Cogliani, C. et al (2011). p.277
[282] Cogliani, C. et al (2011). p.277
[283] Public and International Health Directorate (2016). p.11
[284] Grace, K. et al. (2014). p.19
[285] Grace, K. et al. (2014). p.19
[286] Public and International Health Directorate (2016). p.11
[287] Grace, K. et al. (2014). p.11
[288] Grace, K. et al. (2014). p.11
[289] Grace, K. et al. (2014). p.11

weight.[290] This system allows for statistics to be easily compared between the other EU member states.[291]

In 2014, 57mg/PCU of antibiotics sold for use in food-producing animals, increasing slightly from 2013, where 56mg/PCU was sold.[292] Macrolides, fluoroquinolones, cephalosporins and glyco-peptides have been classed as vital antibiotics according to the WHO.[293] 0.20mg/PCU of 3rd and 4th generation cephalosporins and 0.34mg/PCU of fluoroquinolones were sold for use in production animals in 2014, levels of which are low compared to other antibiotic groups.[294] In 2013, out of 30 member states the United Kingdom was rated 22nd for resistance to 3rd generation cephalosporins and 9th for resistance to fluoroquinolones.[295] In 2013, the highest sold antibiotics in human and veterinary medicine were both penicillin's and tetracyclines.[296] However, the stability of the general mg/PCU in production animals for both cephalosporins and fluoroquinolones is fixed.[297]

6.3.5 Progress in the Netherlands

The Netherlands approach to dealing with antibiotic resistance differs from Denmark and the United Kingdom.[298] Initially, the Dutch attempted to implement regulations without a plan, therefore, when the ban came about the farmers were unprepared.[299]

In 1999, a programme called MARAN was formed to survey antibiotic resistance in food and animal organisms.[300] In 2006, Dutch sales data showed the inhibition of growth promoters caused the therapeutic use of antibiotics to increase.[301] Reasons for the increased use of antibiotics may have included; expansion of farms, improper control measures, insufficient government supervision of antibiotic use and sales and reluctance of farmers to implement changes.[302] Antibiotics were still being used unnecessarily and

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290 Hopkins, S. and Muller-Pebody, B. (2015). p.29
291 Grace, K. et al. (2014). p.11
292 Grace, K. et al. (2014). p.11
293 Hopkins, S. and Muller-Pebody, B. (2015). p.12
294 Grace, K. et al. (2014). p.11
295 Hopkins, S. and Muller-Pebody, B. (2015). p.31
296 Hopkins, S. and Muller-Pebody, B. (2015). p.12
297 Grace, K. et al. (2014). p.20
298 Cogliani, C. et al (2011). p.275
299 Cogliani, C. et al (2011). p.275-276
300 Cogliani, C. et al (2011). p.276
301 Cogliani, C. et al (2011). p.276
302 Cogliani, C. et al (2011). p.277

inappropriately to treat diseases, improve the food conversion ratio and to treat non-infectious diseases.[303]

Netherlands have shown that inhibiting the use of growth promoters, must be accompanied by a well-structured and well-executed plan for the effective implementation of their strategies, including surveillance, monitoring, research and efficient control measures.[304] After this failure, the Danish government interceded.[305]

The most recent report states that the sales in 2013 for antibiotic use in animals was 69.9mg/PCU, showing a reduction of 52% from 2010 to 2013.[306] The objectives set by the government for animal production are mostly concentrated on four areas that make up 87% of the antibiotic use in the Netherlands; dairy cattle, pigs, broilers and veal calves.[307] In the pig industry, between 2009 and 2015, there was a substantial decrease of 56% in the use of antibiotics in pig farms, with no important human antibiotics being utilised.[308] A new strategy for pig farmers is existing for the period 2016-2020. The strategy involves farmers developing a better farm management, offering incentives like market rewards for low usage of antibiotics and supplying more aid to farmers who have a high use of antibiotics.[309] In the veal industry, since 2010 there has been a 44% decrease in antibiotic use, with 1st choice antibiotics being the most consumed.[310] Overall, there has been a 26% decrease in antibiotic resistance in veal calves in the Netherlands.[311] The veal industry has also implemented a new strategy, to have higher quality calves with an improved standard of health.[312] This strategy should to be achieved via cooperation between the parties involved and improved research within the industry.[313]

In broilers, better control of antibiotic utilisation has seen a reduction in antibiotics used when new flocks arrive to farms from 68% to 8% in the period between 2010 and 2015, similarly after vaccinations less antibiotics were required, falling from 41% to 4%.[314] However, in 2015 it was found that there was a 17% increase in antibiotic use in

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303 Cogliani, C. et al (2011). p.277
304 Cogliani, C. et al (2011). p.277
305 Cogliani, C. et al (2011). p.276
306 European Commission (2016). p.5
307 European Commission (2016). p.12
308 European Commission (2016). p.16
309 European Commission (2016). p.16
310 European Commission (2016). p.15
311 European Commission (2016). p.15
312 European Commission (2016). p.15
313 European Commission (2016). p.15
314 European Commission (2016). p.20

Turkeys, something which must be addressed by the government.[315] In January 2016, rabbit producers voluntarily joined the same initiative, with the aim to reduce the utilisation of antibiotics by 70% in the period between 2011 and 2018.[316]

In 2017, the government have suggested that they will become more lenient on their regulations regarding the use of 2nd choice antibiotics:[317]

- It will now be acceptable for the farmer to contact the veterinarian by phone to request the use of 2nd choice antibiotics, instead of the veterinarian making a visit to the farm.[318]
- 3 farm-specific diseases must be specified for the use of 2nd choice antibiotics.[319]
- The farm is only allowed enough 2nd choice antibiotic present on their farm to treat 5% of veal calves, 10% of dairy calves and 10% per house of piglets.[320]

In 2011 to 2012, the sale of 3rd and 4th generation cephalosporins reduced by 94% and for fluoroquinolones the sales decreased by 45%.[321] In 2013, cephalosporins were 0.01% of the total sales of antibiotics and fluoroquinolones were 0.2%.[322] The sale of prescription medicines with colistin as the active ingredient, decreased by 68% between the period of 2011 to 2015.[323] However, the rate of reduction of antibiotic use in food-producing animals is becoming even, with a drop of only 0.65% in 2015, therefore the Danish government will need to improve their policies to further eliminate antibiotic resistance.[324]

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[315] European Commission (2016). p.5
[316] European Commission (2016). p.12
[317] European Commission (2016). p.12
[318] European Commission (2016). p.12
[319] European Commission (2016). p.12
[320] European Commission (2016). p.12
[321] European Commission (2016). p.5
[322] European Commission (2016). p.5
[323] SDa (2016). p.24
[324] European Commission (2016). p.5

7. Recommendations

In order to reduce antibiotic use and resistance, compliance is required globally. The most efficient way of succeeding against resistance is prevention as, “prevention is better than a cure” (FVE, 2016). The best preventative methods include;

1. Improving biosecurity practices within farms is a key responsibility in antibiotic resistance.[325] Bio-exclusion and biocontainment are the major components of biosecurity and are important for keeping diseases out of a farm and reducing the risks of diseases on farms.[326] Biosecurity can be enhanced via improving housing through better hygiene and ventilation to reduce the presence of microorganisms.[327] Hygiene can be improved via the use of disinfectants, providing protective clothing, cleaning facilities and foot baths for visitors to farms. An example of biosecurity that has proven successful in many farms especially piggeries and poultry farms, is the all-in-all-out method.[328] The implementation of this method should be considered across the board.

2. Frequent visits from the farms veterinarian is recommended.[329] Regular visits are important in order for the veterinarian to create a relationship with the farmers.[330] This allows for trust to develop in order for the veterinarian to educate the farmer and to familiarise themselves with the farm and the animals, enabling the veterinarian to create a specific herd health plan catered to the needs and financial position of each farm.[331] Its highly essential to educate farmers to prevent the misuse of antibiotics on farms and also to ensure their compliance with the herd health plan as it can only be successful if all parties comply.[332]

3. The development of a herd health plan should include vaccine strategies, and is considered an essential preventative method. The vaccines should cover both

[325] FVE (2016). p.13
[326] AHI (2016)
[327] FVE (2016). p.13
[328] FVE (2016). p.13
[329] FVE (2016). p.14
[330] FVE (2016). p.14
[331] FVE (2016). p.14
[332] European Medicines Agency (2011). p.9

bacterial and viral infections.[333] An initiative called the certification system has been promoted in which animals are fully vaccinated and kept in excellent conditions, meaning producers will pay more for these animals, but in the long-run will pay less on veterinary fees.[334] For global co-operation, vaccines should be made available to each country, especially due to global trade of livestock and meat products it's important to cover diseases that occur in a number of countries.[335]

4. An advancement in diagnostics is crucial in order to tackle antibiotic resistance. Improved diagnostics can reduce the number of antibiotics prescribed by veterinarians and especially reduce the incorrect use of antibiotics.[336] Particularly helpful diagnostic instruments are antibiotic susceptibility tests (ASTs), allowing for a prompt analysis within 30 minutes.[337] There are two types of ASTs; phenotypic and genotypic.[338] The genotypic AST detects genetic markers for example, plasmids, mutations or genes.[339] The difficulty with this type of AST is that it needs extensive knowledge to determine which markers need to be tested and if new mutations occur, it would cause a false negative result.[340] Phenotypic ASTs detect different bacterial growth on solid agar plates or in liquid cultures.[341] This AST detects the resistance of the bacteria to particular antibiotics, establishing the most suitable antibiotic to be used.[342] The biggest advantage in using ASTs is that narrow spectrum antibiotics can be used, preventing the use of broad spectrum antibiotics.[343]

5. Genetic selection and advanced breeding programs should be a focus worldwide, in order to develop robust animals.[344] The animals chosen for breeding should not only have a high production output but should also have a low susceptibility to

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[333] FVE (2016). p.14
[334] FVE (2016). p.17
[335] FVE (2016). p.15
[336] FVE (2016). p.15
[337] Baltekin, Ö. *et al.* (2017). p.9170
[338] Baltekin, Ö. *et al.* (2017). p.9170
[339] Baltekin, Ö. *et al.* (2017). p.9170
[340] Baltekin, Ö. *et al.* (2017). p.9170
[341] Baltekin, Ö. *et al.* (2017). p.9170
[342] Baltekin, Ö. *et al.* (2017). p.9170
[343] Baltekin, Ö. *et al.* (2017). p.9170
[344] FVE (2016). p.16

diseases, this would require more attentive monitoring from farmers to ensure a successful breeding program.[345]

6. It has been recommended by WHO that each country should create surveillance programmes to collect data on antibiotic sales and utilisation.[346] It's also important to monitor bacteria from human beings, production animals and meat, allowing surveillance on the spread of bacteria in meat and meat products.[347] However, in order for surveillance to be successful on a global level, it is vital that the strategies on which the data is collected, are uniform.[348] WHO has established the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (WHO-AGISAR), which assist WHO in their surveillance, revise the list of important antibiotics and also work with other bodies such as OIE and FAO to have a successful global surveillance plan.[349] Effective programmes will allow veterinarians to be informed when diseases are transpiring, in order to take measures and develop preventative plans.[350]

In the long-run prevention will enhance production and will develop and improve food safety, which is crucial for public health.[351]

[345] FVE (2016). p.16
[346] WHO (2014). p.61
[347] WHO (2014). p.61
[348] WHO (2014). p.61
[349] WHO (2014). p.61
[350] FVE (2016). p.16
[351] FVE (2016). p.13

8. Conclusion

Antibiotics have enhanced human medicine of today and have saved countless lives. They are highly limited and are becoming less effective due to their overuse.[352] The unnecessary and inappropriate use of antibiotics is putting the public at risk and allowing the development of antibiotic resistance, leading to treatment failure especially of life-threatening illnesses.[353]

Antimicrobial resistance is a natural process and has been known about for decades.[354] However, our knowledge has since improved, especially about the mechanisms of resistance which can help in the development of new agents such as, plant derived antimicrobials.[355] It's important that we use our knowledge not to create new antibiotics, which would cost a lot of time and money, but to educate producers about resistance and that prevention is better than treatment.

Reduction in antibiotic use will require the efforts of everyone in order to succeed.[356] It will entail the full cooperation of all parties to implement strategies and plans and to promote proper prescribing and use of antibiotics in both veterinary and human medicine.[357] It's also important that the same strategies and principles are implemented across the globe and that all governments are fully cooperative with the principle bodies such as WHO, OIE and FAO.[358] The promotion of surveillance and monitoring is also important in tackling antibiotic resistance with the view to using the data collected for future strategies, innovation, and educating both professionals and producers about the advantages and risks of antibiotics use.[359] When all parties play their roles to improve antibiotic use, public health is conserved and antibiotics will be available for life-saving illnesses for future generations.[360]

[352] CDC (2017). p.35
[353] CDC (2017). p.35
[354] Blair, J. M. A. et al. (2014). p.48
[355] Blair, J. M. A. et al. (2014). p.49
[356] CDC (2017). p.35
[357] CDC (2017). p.35
[358] CDC (2017). p.35
[359] CDC (2017). p.35
[360] CDC (2017). p.35

9. Summary

The following is a literature review on how the abuse and inappropriate use of antibiotics by both professionals and producers of food-producing animals has had an impact on human medicine, due to antibiotic resistance. It details the implications that the overuse of antibiotics has had on bacteria causing human diseases, including E. coli and MRSA. It also shows the repercussions that will occur in the future if changes cannot be made or if alternative therapies cannot be found.

The review outlines the mechanisms of the resistance and how the resistant bacteria spread from the environment to, and between individuals, resulting in the eventual transmission to the public via the food chain. The mechanisms are displayed, in depth, how the bacteria develop and acquire resistance via a number of methods based on genetics or mechanics.

The highly critical groups of antibiotics used in human medicine are highlighted here, and are those which are most affected by their overuse. These critical antibiotics have corresponding bacteria that are resistant to their actions and that cause human illnesses, therefore, having an effect on the welfare of the public and future generations. Comparisons are offered in the utilisation of antibiotics and the strategies implemented in different countries worldwide, in order to reduce antibiotic resistance. The success of these strategies, are presented based on the current sales records of each country and how much the sales have declined since the previously recorded sales.

Recommendations and alternatives to antibiotics are also suggested in the review in order to tackle the issue of antibiotic resistance. The recommendations include improvements that farmers can implement on their farm including improved herd health via nutrition, vaccines and hygiene. Alternatives put forward, have been proven to work against harmful bacteria and should be explored more as another option for producers to reduce the occurrence of resistant bacteria within their livestock.

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