Antimicrobial resistance: an agent in zoonotic disease and increased morbidity.

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Abstract

The emergence of antibiotic resistant organisms is a significant challenge where increasing numbers of bacterial species are now showing multidrug resistance. At government level, there is a global incentive to develop novel therapeutic options; however, the development of new antibiotic agents will undoubtedly be followed by the emergence of resistance to these compounds, implying that the use of antibiotics is unsustainable. Currently there is a lack of new antibiotic options available for use especially against Gram negative pathogens. Reduction in the use of antibiotics and the prevention of infection therefore, may prove the most useful method to combat the issue. The use of antibiotics for veterinary applications as therapeutic, prophylactic, metaphylactic and as animal growth promoters has greatly proliferated the problem. The presence of sub-therapeutic levels of antibiotics in water ways from both agriculture and aquaculture encourages the expression of drug resistance. Furthermore, their high water solubility, extensive half-lives and constant use means that they persist in the environment, having repercussions for human and ecological health. The use of antibiotics from an early age may also have a negative impact on human morbidity with potential to contribute to obesity, dysbiosis and target organ toxicity of the liver and kidneys. This review aims to discuss three main concerns 1) the extensive use of antibiotics for veterinary and its impact on the emergence of resistance, 2) the occurrence of zoonotic disease particularly with resistant strains and 3) the relationship between both aquatic and food pollution and human morbidity.

Keywords: antibiotic resistance, veterinary, public health, food pollution.

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Introduction

Antimicrobial resistance (AMR) and its relationship to human and animal morbidity is one of the biggest challenges facing modern medicine. The extent of the problem is now so great that the World Health Organisation (WHO) has published a priority list of antibiotic resistant pathogens based on critical, high and medium risk. The emergence of antimicrobial resistance in bacterial species is an evolutionary process which has been proliferated by the improper use and overuse of therapeutic agents. Over the counter purchasing and prescribing antibiotics where bacterial species are not the causative agent of disease are both major contributors to AMR. Moreover, the use of antimicrobials in veterinary medicine for disease treatment and prevention in both domestic and non-domestic animals also contributes significantly to the issue. Additionally, antibiotics (ABs) are widely used as growth promoters in aquaculture [1] and for promoting the faster growth of livestock in agriculture [2]. Bacterial species gain antibiotic resistance through several mechanisms such as mutational alterations of antibiotic targets, changes in cell permeability, drug efflux and horizontal gene transfer coding for resistance [3]. The prolonged infection of patients not responsive to therapeutic treatment is a serious health hazard resulting in extended hospital stay, increasing economic costs while also increasing the spectrum of resistance as more and more drug types are prescribed. Studies have shown that almost 70% of categorised nosocomial infections are resistant to at least one clinically relevant antibiotic [4] with many strains exhibiting multidrug resistance (MDR) to many classes of antibiotics. Furthermore, the nature of the bacterial resistance mechanisms of pathogens means that AMR and MDR will remain an on-going problem even with the development of new chemotherapeutic agents. For this reason, it is important to look at ways to control and reduce the spread of such pathogens where possible. The transmission of pathogenic and resistant bacterial species to human hosts from companion animals plays an important role in human morbidity. Zoonotic transmission and disease presents as an area that may allow for some improvement or reduction in the rate of emerging resistant species. For this reason, this review aims to outline the predominant resistant species associated with veterinary clinics and the role of AMR in zoonotic disease.

Mode of Resistance

The modes of resistance for the most relevant zoonotic species are outlined in Table 1 for antibiotics commonly employed for veterinary uses.

Resistance in Veterinary

The use of antibiotics in the veterinary industry relates to the treatment of animals and to the production of animal based food products. Agricultural use of antibiotics can be categorized into four uses: therapeutic use, prophylactic use for disease prevention, metaphylactic use for infection control and as animal growth promoters (AGPs) [28]. For these purposes food-

Table 1: *Summarising the modes of resistance of species relevant to zoonosis and the veterinary application of antibiotics.*

Antibiotic	Modes of Resistance	Resistant Strains	References
Inhibition of Cell Wall Synthesis			
Beta-lactams			
Penicillin's: ***Natural:*** penicillin G, penicillin V ***Extended-spectrum penicillin:*** amoxicillin, ampicillin, carbenicillin **Cephalosporins:** ***1st- generation cephalosporins:*** Cefadroxil, cephalexin ***3rd - generation cephalosporins:*** Cefovecin, cefpodoxime, ceftiofur ***4th- generation cephalosporins:*** Cefquinome **Carbapenems:** Primaxin **Beta-lactamase inhibitors:** Clavulanic acid, sulbactam	Production of β-lactamases i.e. Enzymatic degradation; Alteration of new penicillin binding proteins (PBP); Decreased uptake i.e. Porin channel formation is decreased Bind β-lactamase enzymes	*Klebsiella pneumoniae*, *Acinetobacter baumanii, Pseudomonas aeruginosa*, *Salmonella Typhimurium DT 104,* (ESBL)-producing Enterobacteriaceae*, Enterococcus faecium*, *Pasteurella* spp., *Brucella* spp., *Staphylococcus aureus*, *Clostridium difficile, Campylobacter spp.*	[5] [6] [7] [8]
Inhibition of cell membrane function			
Polymyxins			
Colistin (Polymixin E), Polymixin B	Lipopolysaccharide (LPS) modifications - covalent modifications of the lipid A moiety of LPS Drug efflux	**Enterobacteriaceae spp.***; Pseudomonas aeruginosa*, *Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Salmonella enterica, Acinetobacter baumannii*	[9] [10]
Inhibition of Protein Synthesis			
Macrolides			
Erythromycin, Tylosin and spiramycin, Tilmicosin, Tulathromycin	Target site modification i.e. binding to the 50S subunit of the ribosome Horizontal Gene transfer Drug efflux	*Enterococci spp. (E. faecalis, E. faecium), Campylobacter spp*, *M. Bovis,* *Pasteurella multocida, Mannheimia haemolytica*, *Bartonella* spp., Most gram-negative organisms	[11] [12]
Lincosamides			
Lincomycin, Clindamycin and Pirlimycin	Target site modification i.e. binding to the 50S subunit of the ribosome Horizontal Gene Transfer Drug efflux	*Campylobacter* spp., *Pseudomonas aeruginosa, Acinetobacter, Staphylococci, Enterococci, Pasteurella multocida, Mannheimia haemolytica, Escherichia coli,*	[12]
Aminoglycosides			
Amikacin Gentamicin Streptomycin Neomycin Kanamycin, Tobramycin	Cell membrane modification - decreased permeability Alterations at the ribosomal binding sites Production of aminoglycoside modifying enzymes (AMEs). Drug efflux	*Salmonella Typhimurium DT 104, Klebsiella* spp., *Acinetobacter baumanii, Escherichia coli, Pasteurella spp., Campylobacter spp., S. aureus, Enterococci spp. (E. faecalis)*	[13] [6] [14] [15] [16]
Chloramphenicol	Target site modification i.e. binding to the 50S subunit of the ribosome Enzymatic inactivation by acetylation by chloramphenicol acetyltransferases (CATs) Drug efflux	*S. aureus, Salmonella Typhimurium DT 104, Pseudomonas aeruginosa*, *Proteus spp.*, *Klebsiella* spp, *Campylobacter* spp., *Escherichia coli, Enterococci spp. (E. faecalis)*	[6] [17]
Florfenicol (fluorinated analog of thiamphenicol)	Target site modification Drug efflux - Over-expression of antimicrobial efflux pumps Horizontal Gene Transfer i.e. Acquisition of transferable resistance determinants	*S. aureus*, *Salmonella Typhimurium DT 104, Klebsiella* spp., Acinetobacter spp., *Escherichia coli, Pasteurella piscicida*	[18] [19] [20]
Tetracyclines			
Chlortetracycline Doxycycline Oxytetracycline Tetracycline	Protection of ribosomes Enzymatic inactivation Drug efflux	*Pasteurella spp., Pseudomonas spp., S. aureus Salmonella Typhimurium DT 104, Brucella* spp., *Campylobacter* spp., *Klebsiella spp., Escherichia coli, Acinetobacter baumanii, Enterococci spp. (E. faecalis)*	[21] [22] [23] [24]

Inhibition of DNA Function			
Quinolones & Fluoroquinolones			
Ciprofloxacin, Danofloxacin, Difloxacin, Enrofloxacin, Marbofloxacin, Norfloxacin, Orbifloxacin, Pradofloxacin	Mutational alterations in target enzymes – DNA gyrase and topoisomerase IV Horizontal gene transfer Drug efflux	*Escherichia coli, E. faecium, Neisseria gonorrhoeae, Campylobacter spp (C. jejuni and C. coli), Salmonella Typhimurium DT 104, Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter baumanii*	[25] [6] [26] [27]
Sulphonamides			
Sulfadiazine, Sulfamethoxazole, Sulfadoxine	Alteration of Enzyme (dihydropteroate synthetase) Over-production of para-aminobenzoic acid (PABA) - inhibition of dihydropterate synthetase enzyme Horizontal gene transfer	*Pasteurella spp. Salmonella Typhimurium DT 104 Neisseria meningitidis, Pseudomonas aeruginosa, Campylobacter* spp., *Bacillus* spp., *Escherichia coli, Shigella., Klebsiella*	[22] [6] [20] [18]

producing animals are given the same classes of antibiotics used for human therapeutics increasing the emergence of resistant bacterial species to the antibacterial agents.

Agriculture and Aquaculture Use of Antibiotics

Some of the most commonly used antibiotics in veterinary include tetracyclines as growth promoters and therapeutics in cattle, beta-lactams, chepalosporins and macrolides for disease treatment and growth enhancement and peptidomimetics as growth promoters in poultry [29]. In the 1980s the first older generation quinolones (oxolinic acid and flumequine) were licensed for use in food producing animals, with fluoroquinolones being used as growth promoters in the late 1980's and early 1990's. This use of antibiotic agents means that large amounts of antibiotics and their metabolites which may still be active are excreted by the animals daily [30]. The presence of these active antibacterial agents may then have effect on the micro biota of the soil, enter ground water, be re-consumed by livestock and/or gain entry to drinking water supplies. The spreading of animal manure as a fertiliser also contributes to this antibiotic pollution as it harbours large numbers of potentially resistant bacteria and is prone to agricultural run-off in to surrounding waterways. Furthermore, the nutrients present in the manure stimulate microbial growth and horizontal gene transfer between the different species present [30]. The use of antibiotics in aquaculture is to control infection and to increase productivity, where salmonids, catfish and lobsters are given FDA approved drugs such as sulfadimethoxine, ormetoprim, and oxytetracycline via medicated feeds [28]. The sub-therapeutic concentrations of these antibiotics used in aquaculture are mostly encountered after their prophylactic use [4]. This sub-therapeutic concentration means that fish feed and faeces present in the surrounding aquatic environment allows for the promotion of AMR by exposing bacteria to low concentrations that can select for resistance. Furthermore, fish do not metabolise antibiotic drugs effectively and so excrete them in their active form into the environment. The presence of antibiotic agents in the meat from harvested fish and other farmed animals is now a reality as drug residues persist in animal tissues [31] resulting in contaminated food supplies and increase in AMR.

Emergence of AMR in Veterinary

Bacterial species associated with agriculture food producing animals and are *Campylobacter jejuni, Salmonella enterica, Typhimurium* DT104, and *E. coli* O157:H7 [4]. *Salmonella* and *Vibrio* are potential pathogens associated with aquaculture with *Listeria monocytogenes, Aeromonas*, and *Clostridium spp*. being recognised as emerging threats [2]. The use of fluoroquinolones particularly ciprofloxacin in poultry production since 1995 led to the emergence of ciprofloxacin resistant bacteria *Campylobacter*, which was subsequently detected in the breast meat of sacrificed animals. The antibiotic avoparcin which is used as an AGP in veterinary is believed to also promote vancomycin resistance, with the AGP antibiotic vinginicmycin having a similar affect with streptogramin which is used for human medicine [32]. Cross resistance such as this occurs when a specific drug influences bacterial resistance and susceptibility to other antibiotics and happens regularly between antibiotics of the same class e.g. resistance between extended spectrum b-lactamases (ESBLs) caused cross-resistance within the class of penicillins and cephalosporins [33]. Resistance modes of action based on altered efflux pumps and enzymatic degradation via gene sharing enables this cross resistance to occur over different classes of antibiotics, allowing resistance mechanisms developed to antibiotics solely used in veterinary to proliferate AMR to other antibiotics classes. Ceftiofur and cefquinome are third and fourth generation cephalosporin's exclusively used as veterinary medicines [34] for the treatment of mastitis caused by *Staphylococcus aureus*, with ceftiofur also used prophylactically in piglets to prevent arthritis, meningitis, septicemia, and diarrhea [35]. This use of cephalosporins has resulted in the emergence of ESBL producing *E. coli* which is transmissible to human hosts via excretion into the environment. Colistin also known as polymyxin E is an antibiotic used for the treatment of MDR gram negative pathogens and specifically for the carbapenemase producing Enterobacteriaceae since the 1990s. Colistin was banned from human use in the 1970s due to its nephrotoxic effect on the kidneys but remained in use as prophylactic and as a growth promoter in pigs [36]. Resistance to colistin has now emerged in *Klebsiella pneumonia*, an important human pathogen that causes hospital-acquired and community-acquired infections [37].

Treatment Options and Methods to Reduce AMR

To reduce the proliferation of AMR the European Union (EU) banned the agricultural use of antibiotics as growth promoters in 2006. The dose administered for this purpose is typically sub-therapeutic and as a result serves to promote resistance in bacterial species. In countries such as America, Canada and Asia

however, this ban has not been implemented where antibiotics are continually used for agricultural purposes [38]. Indeed, in developing countries such as China and India where the use of antibiotics is not regulated and antibiotics are supplied as over the counter (OTC) medicines the rates of resistance are high [39]. Furthermore, the use of quinolones for aquaculture was banned in several industrialized countries, as AMR to one type of quinolone typically results in resistance to all members of this class of antibiotics [2]. Reducing antibiotic pollution caused by both agriculture and aquaculture will aid in reducing the number of environmental bacteria having acquired resistance mechanisms. In the EU an environmental risk assessment (ERA) is compulsory for therapeutics with an expected environmental concentration exceeding 10 ng/L with 100 ng/L being the ERA in the USA [1]. There is a need for novel antibiotic agents which have effect on the already AMR and MDR strains however; undoubtedly resistance mechanisms will emerge to any new therapeutic developed. Additionally, exposure to sub-therapeutic levels of antibiotics interferes with some important physiological processes of bacterial cells which can result in changes in bacterial virulence as well as resistance [40] increasing their pathogenicity. The use of efflux pump inhibitors given in conjunction with AB agents can prevent resistance by interfering with the proton motive force of the resistant strain or by competing with the binding site of the pump itself [41]. Research at present is on-going assessing the potential for nanomaterials such as titania dioxide (TiO_2) and graphene oxide (GO) as antimicrobial surface coatings [42]. The application of bacteriophages as antibacterial agents is also a possibility as phage's causes specific bacterial cell death while not affecting the animal host.

Zoonotic Disease Transmission of AMR

Summarising incidents of zoonotic disease from veterinary AMR bacterial and fungal species in Table 2.

Table 2: *Summarising incidents of zoonotic disease from veterinary AMR bacterial and fungal species; T – Therapeutic, P – disease prevention (prophylactic/metaphylactic), GP – growth promotion.*

Antibiotic	Use in Veterinary	AMR	Zoonotic Disease	References
Bacterial species				
β-lactams; Cefotaxime, Cephalexin **Macrolides;** Erythromycin, Clarithromycin, Tylosin, Azithromycin, Ketolides e.g., telithromycin **Aminoglycoside;** Kanamycin, Gentamicin **Tetracyclines** **Chloramphenicol Streptogramin B** **Quinolones/Fluoroquinolones;** Ciprofloxacin, Norfloxacin, nalidixic acid **Bacitracin** Rifampin **Sulphonamides;** Trimethoprim-sulfamethoxazole **Vancomycin**	T, P, GP T, P, GP T, P T, P, GP T T, P, GP T, P T, P, GP T T, P, GP T, P, GP	***Campylobacter* spp.;** *E. coli* and *C. jejuni*	Campylobacteriosis	[43] [44] [45] [46]
β-lactams; Amoxicillin-Clavulanic acid, Ampicillin, Cephalothin; Cefotaxime **Macrolides;** Azithromycin; **Chloramphenicol** **Aminoglycoside;** Gentamicin, Streptomycin; Kanamycin; **Tetracycline**; Oxytetracycline; Sulphonamides; Sulfamethoxazole; Trimethoprim-sulfamethoxazole; **Quinolones/Fluoroquinolone;** Norfloxacin	T, P, GP T, P, GP T T, P T, P, GP T, P, GP T, P	**Verocytotoxin (VT)/ Shigatoxin (ST)-producing *Escherichia coli* (VTEC/ STEC);** *E. coli* O157:H7 (most common)	Haemorrhagic colitis (HC); Thrombo-cytopenia; Haemolytic uremic syndrome (HUS)	[16] [47] [48]
β-lactams; ampicillin, cephalothin, amoxicillin-clavulanic acid, cefmetazole, cefotaxime; Penicillin G, **Quinolones/Fluoroquinolones;** enrofloxacin, ciprofloxacin **Sulphonamides**; trimethoprim/sulfamethoxazole, **Aminoglycoside**; gentamicin Tetracycline **Chloramphenicol** **Polymyxins**; Colistin Sulphate	T, P, GP T, P T, P, GP T, P T, P, GP T T, P, GP	***Klebsiella spp.;*** *K. pneumoniae and ESBL-producing K. pneumoniae*	Septicemic, Pneumonic, Urinary Tract Infections (UTIs)	[49] [50]
Aminoglycoside; Amikacin, Gentamicin, Tobramycin **β-lactams;** Cefoperazone, Cephalothin, Cefoxitin, Piperacillin, Cefotaxime, Ampicillin-sulbactam, Imipenem, Ticarcillin, Mezlocillin, Carbapenems **Tetracycline;** Doxycycline, Minocycline **Quinolones/Fluoroquinolones;** Ciprofloxacin, Levofloxacin	T, P T, P, GP T, P, GP T, P	***Acinetobacter baumanii***	Skin and soft tissue infections, Ventilator-associated pneumonia, Bacteraemia	[51] [52] [15]
β-lactams; Cefazolin, Ampicillin, Cephalothin **Lincosamides;** Clindamycin, Lincomycin **Sulphonamides;** Sulfamethoxazole-Trimethoprim Chloramphenicol	T, P, GP T, P T, P, GP T	***Pseudomonas aeruginosa***	Pneumonia, Septicaemia, Osteomyelitis	[53]
Fungal species				
Azoles; Itraconazole, Fluconazole	T, P	**Candida spp.** *C. albicans, C. tropicalis, C. krusei, C. parapsilosis sensu lato,*	Candidiasis	[54] [55] [56]
Azoles; Fluconazole	T, P	***Cryptococcus* spp.** *Cryptococcus neoformans*	Cryptococcosis	[57]

Influence on Morbidity

The presence of antibiotic drug residues in food products coming from agriculture and aquaculture poses a threat to public health safety as such contamination is typically unrecognised. Additionally, the contamination of water supplies from agricultural runoff and waste water adds to the concentration of drug available for human consumption. Fat soluble antibiotics such as tetracycline and sulphonamides may also bio-accumulate in animal tissue where they then become a food pollutant [2]. There is little information available on the effect of these compounds, the rate of bioaccumulation and incidence of morbidity in humans and animals. The presence of antibiotic contamination in dairy products and their role in triggering allergic reactions is one such possibility [58]. Penicillin is an antibiotic with little toxicity except for cases of allergic reactions where anaphylactic shock is high risk. The presence of penicillin in dairy products is therefore of concern for persons presenting with allergies towards this drug. Additionally, antibiotics are known to have adverse effects on both the liver and kidneys however; little information is available on their effects on mammalian cells and human toxicity [59]. Injury to the liver caused by antibiotics manifests as hepatitis caused by isoniazid and sulphonamides, cholestasis from macrolides and penicillin's and steatosis caused by tetracycline. Potentially, toxic effects could be found in treated animals, animals exposed to environmental contamination and incidental uptake and humans exposed from food contamination or zoonotic transmission. Dysbiosis an imbalance of the microbiota of the gastrointestinal tract (GIT) in animal and humans following consumption of antibiotics is also a possibility. This imbalance in gut microbiota leaves the patient susceptible to gastrointestinal infections; antibiotic associated diarrhoea (AAD) and can lead to colitis of the GIT. Microbial species associated with such dysbiosis and antibiotic depletion of the gut microbiome include *Klebsiella pneumoniae, Staphylococcus aureus and Clostridium difficile* [60]. *C. difficile* infection often results in patient mortality and is frequently associated with the use of clindamycin, cephalosporin or fluoroquinolones, and the microbiota of patients with *C. difficile* infection has a diminished natural diversity [19]. Immunocompromised persons and neonates are particularly at risk from AMR and untreatable infections. Colonisation of the GIT by vancomycin-resistant *Enterococcus* has been shown to precede bloodstream infection in immunocompromised patients, where experimental work in mice established that antibiotic treatment plays a role in the intestinal outgrowth of this bacterium [61]. Additionally, an alteration in the gut microbiome can have a negative effect on the immune system of the host. Commensal gut microbes are in close contact to intestinal epithelial cells where a barrier prevents commensal and pathogenic microorganisms entering into the gut lumen. These epithelial cells and paneth cells also secrete antimicrobial peptides (AMPs) [62] which play an important role in immunity. Depletion of the gut microbiota and an over growth of a non-commensal AMR strains can have a deleterious impact on this function. Epidemiological studies have shown a correlation between the use of antibiotics and childhood obesity which is also accompanied by an increased risk of metabolic and cardiovascular disease, musculoskeletal problems as well as psychosocial issues [63]. Studies report that the administering of antibiotics to children in infancy [64,65] is related to a higher body mass index (BMI) and an increased risk of obesity [65] throughout childhood.

Conclusions

The over use and misuse of antibiotics over the last number of decades has generated a serious problem with no immediate solution in sight. Human infection with antibiotic resistant bacterial species has increased patient morbidity and mortality rates globally. The presence of these drug compounds in waterways and foods has resulted in both water and food contamination at levels currently unknown. It is of the upmost importance to determine the effect of such contamination on human morbidity and public health safety. Measures must also be taken to slow the rate of emergence in currently treatable bacterial species. The use of antibiotics for the treatment of conditions, which are not of bacterial origin or in cases where there is little or no evidence of efficacy has greatly proliferated AMR. In order to control the increasing rate of bacterial species gaining resistance, measures must be taken to limit the use antibiotics as both human and veterinary therapeutics. This is important not only from an AMR perspective but also to ensure public health safety where there is increasing evidence linking antibiotics to human morbidity especially in infants. Several studies have shown that the zoonotic transmission of infectious pathogenic microbial species is a serious cause of human disease. Furthermore, the impact of bacterial resistance and the increasing loss of antibiotic effectiveness is a significant challenge for both animal health and public health safety. With the aim of reducing AMR the EU implemented a ban in 2006 on the use of antibiotic growth promoters; this was not implemented however, by other countries such as China and the USA.

Conflicts of Interests

The authors declare no conflict of interest.

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