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Antibiotic resistance in animals

A report for the APVMA

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Preamble

It was in 1929 that Alexander Fleming discovered that an obscure mould on a glass plate in his laboratory could kill bacteria (Fleming 1929). But it was Australian scientist Howard Florey working at Oxford University who isolated the bacteria-killing substance found in the mould and named it penicillin. Nicknamed the 'wonder drug' it heralded the dawn of the antibiotic age. It's difficult to imagine but before penicillin, a simple scratch while pruning your roses could kill you if it became infected. By 1944, with American laboratory help, the antibiotic drug was mass produced and saved the lives of tens of thousands of war injured. Since then it and its derivatives have saved millions of people globally.

However, within four years of penicillin's introduction as a therapeutic, infections resistant to the drug were beginning to appear. While new antibiotics were successful for a few years, the bugs soon developed resistance to them too. The problem is, we have been overusing antibiotics, over-prescribing them often for illnesses they can't treat anyway. They have also been used by vets to treat animal diseases and by farmers as feed additives because one of their side-effects promotes growth in animals. Over time bacteria have become progressively resistant to more than one class of antibiotic and now doctors and vets are struggling to match the rate at which multi-drug resistant bacteria are developing.

On the front line, the Australian Pesticides and Veterinary Medicines Authority (APVMA) is working to regulate antibiotic use in animals. The Australian Technical Advisory Group on Antimicrobial Resistance (ASTAG), of which APVMA is a member, is using a One Health approach to develop and implement Australia's antimicrobial resistance strategy with the aim of reducing the impact of antibiotic resistance on human and animal health. Although 'antibiotic-free' is not an answer there is an urgent imperative to reduce unnecessary use of antibiotics in humans and animals. Best-practice guidelines and a science-based approach to the responsible use of antibiotics in agriculture are critical in balancing animal welfare and human health. This report documents the global response to antimicrobial resistance (AMR) and describes the APVMA's work in helping to coordinate Australia's human health and veterinary agencies to control it.

Executive Summary

Antimicrobial resistance is a global public health, animal health and welfare concern. Its development and spread is influenced by both human and animal antibiotic use. The APVMA plays a central role in regulating antibiotic use in animals. In this role a principal APVMA objective is to lessen the risk of antibiotic resistance further developing in bacterial populations, particularly where resistance has appeared in antibiotics also used in human medicine. This report addresses the major issues relating to antibiotic resistance associated with the use of antibiotics in animals.

Veterinary antibiotics are medicines used to cure animals of bacterial infection. They are also used controversially in animals as growth promotants and as prophylactics to prevent infections. There is increasing support for a global ban on the use of antimicrobial growth promotants, including from the Australian Veterinary Association (Finance and Public References Committee 2013). Many countries have already banned the use of antibiotics as growth promotants. Some understanding of growth promotants' role in the emergence of resistance to antibiotics important in human medicine arose after enterococci were found to be resistant to glycopeptide and streptogramin antibiotics following their use in animal feeds. Now that avoparcin (a glycopeptide) is no longer used in animals, animal-associated vancomycin resistant enterococci (VRE) is very rarely reported in animals. There has also been a marked reduction in use of virginiamycin. There is concern too about multidrug resistance in zoonotic bacteria such as *Salmonella* and campylobacter and attention is now focussed on multi-drug resistance in *E. coli,* other coliforms and other Gram-negative bacteria. Also concerning is the legal therapeutic use of fluoroquinolones, colistin and 3rd generation cephalosporins in livestock and companion animals in some countries.

International human and animal health agencies have responded in various ways to AMR. In 1998 the Australian Government took an early lead by establishing the Joint Expert Technical Advisory Committee on Antimicrobial Resistance (JETACAR). JETACAR carried out the most comprehensive study at that time in Australia on adverse effects of AMR on humans and in 1999 recommended improvements across human and animal sectors (JETACAR 1999). However, only some recommendations were adopted and in 2013 an Australian Senate Committee called for action on the other JETACAR recommendations. Australia is currently developing a national One Health strategy to reduce the impact of antimicrobial resistance in human and animal health (Department of Health 2015).

Monitoring antibiotic use in agriculture has markedly improved over recent years, as has self-regulation, notably by the pig and poultry industries, and an evidence base for policy development is progressing. However, the emergence and spread of antibiotic resistance remains a priority if antibiotic use is to be regulated effectively. Only then can appropriate regulatory controls be introduced to manage antibiotic use in animals and strategies developed to mitigate antibiotic resistance. Crucially, the Australian Government is now coordinating medical and veterinary regulatory agencies to address animal, human health and environmental issues. One Health is a worldwide strategy, of which Australia is a part, aiming for the collaborative effort of many disciplines to target these issues. Harmonising multinational efforts and harnessing multidisciplinary approaches to disease detection and prevention, the environment and biodiversity, are essential because the health of humans is indivisibly connected with that of animals and the environment.

1 BACKGROUND

In 2001 the World Health Organization (WHO) described AMR as the major global health challenge of the 21st Century. Resistance to antimicrobials is a key issue in treating many human infections including bacterial (eg tuberculosis, staphylococcal bacteraemia, gonococcal infections, multi-drug resistant *Escherichia coli*), protozoan (eg malaria) and viral (eg HIV-AIDS) diseases. Most people would accept that the use of antimicrobials in human medicine is the major driver of resistance development but, in the case of bacterial infections, it is evident that using antibiotics in animals also plays a role, though the data available to date are insufficient to quantify the contribution (EFSA 2017b, EFSA 2017a, Wall et al. 2016). A recent paper by Forslund et al. (2014) demonstrates that antibiotic use both in humans and in animals determines the resistance profile of bacteria in the human gut. In the US more than 70 per cent of antibiotics defined as medically important for humans are sold for use in animals (O'Neill 2016). In this report discussion will be limited to antibiotics, substances that are active against bacteria: antivirals are rarely used in animals (none are currently registered in Australia) and resistance to antifungals and antiprotozoal drugs, such as coccidiostats and ionophores, used in animals although of concern are not as high a priority.

Increasingly we hear that we are entering the post-antibiotic era, a challenging concept when we recognise that antibiotics have only been used in human and veterinary medicine for around 70 years. Although much of the blame is attached to what is called overuse or misuse, any use of antibiotics can lead to the emergence of resistant strains. Another issue is a change in demographics: with increasing use of transplanted organs, significant numbers of people undergoing chemotherapy treatments for cancer, more very premature babies surviving and more people living into their 70s, 80s and beyond, there are more immunocompromised people in the community. More antibiotics are used in these susceptible populations so there is a greater likelihood of resistant strains emerging. We should not be surprised.

Bacteria have been around for nearly four billion years and, as single-celled organisms evolving in very hostile environments, an essential characteristic for survival would have been the capacity to deal with noxious chemicals through mechanisms such as efflux pumps, selective porin channels or inactivating enzymes, and to take rapid advantage of beneficial mutations in binding sites and cellular structures (Blair et al. 2015, Rodríguez-Rojas et al. 2013). Compared with such a history, the advent of human and veterinary clinical use of antibiotics has not provided bacteria with much of a challenge. Also, many of the antibiotics we use originated in soil fungi and bacteria. Bacteria and other microflora sharing the same habitats must have developed antibiotic resistance mechanisms to protect themselves. The ability of bacteria to develop resistance may further increase with ongoing changes in temperature, humidity and weather patterns caused by global climate change. It is worth noting that in studies of DNA extracted from 30,000-year-old permafrost cores, resistance genes to β-lactams, tetracycline and vancomycin were found (D'Costa et al. 2011). Thus Alexander Fleming's comments in his Nobel Prize address in 1945 (before antibiotics were widely used) that resistance is likely to emerge were well-founded (Fleming 1945).

Another important attribute of bacteria is their capacity to share DNA by horizontal transfer (Huddleston 2014). The most important mechanism in terms of antibiotic resistance is conjugal transfer of plasmids and other mobile genetic elements (Carattoli 2013, Iyer et al. 2013). Plasmids carrying resistance genes were first described by Ochiai and co-workers in 1959 (Ochiai et al. 1959) and the extent to which bacteria use this mechanism to share resistance genes has been revealed over the last 50 years (Brown-Jaque et al. 2015, Hawkey & Jones 2009). Resistance genes can also spread through bacterial populations by direct uptake of naked DNA (natural transformation) (Bae et al. 2014, Domingues et al. 2012) and by the action of bacteriophages (transduction) (Shousha et al. 2015, Balcazar 2014).

1.1 Molecular determinants of antibiotic resistance

Over the last 50 years much has been learned about the molecular determinants of resistance but new challenges constantly arise. One new area of particular concern is the rapid emergence of multiple drug resistant bacteria (Davies & Davies 2010) and, in particular, the emergence of Extended Spectrum β-lactamase (ESBL) producing Gram-negative bacteria (Rubin & Pitout 2014). More than 1,300 ESBL enzymes have now been identified and they can be classified into four major molecular groups, further divided into three functional groups (Bush 2013). The enzymes are encoded by families of *bla*[1] genes including *bla*TEM, *bla*SHV, *bla*CTX, *bla*OXA, and *bla*KPC. The enzymes of even more heightened concern are the carbapenemases (eg KPC, OXA, IMP, VIM β-lactamases)[2] which inactivate the carbapenems—the last line treatment for MDR Gram-negative infections in humans. The enzymes that attack the 3rd and 4th generation cephalosporins such as ceftiofur and cefquinome respectively are now often referred to as Extended Spectrum Cephalosporinases (ESCs). A key feature of many of the ESBL/ESC genes is their location on plasmids and other transferable genetic elements (Trott 2013). Resistance to macrolides, such as erythromycin, is an issue with many Gram-positive human pathogens and resistance is usually not confined to the macrolides—but the same genes encode resistance to other related classes of antibiotics such as lincosamides, streptogramins and pleuromutilins in what is described as the MLSB phenotype (Lambert 2012, Roberts 2011) and the PLSA phenotype (Zhang et al. 2015). One key point in relation to aminoglycoside resistance is that the same gene (*aac*(3)-IV) (Herrero-Fresno et al. 2016, Jensen et al. 2006, Johnson et al. 1994) encodes resistance to apramycin and gentamicin. One aminoglycoside inactivating enzyme also inactivates fluoroquinolones. Aspects of aminoglycoside resistance have been reviewed recently (Ho et al. 2014, Ramirez & Tolmasky 2010).

Some examples of resistance mechanisms and determinants for veterinary antibiotics are listed in Table 1. It is worth noting how many multiple modes of resistance to the various classes of antibiotics there are and the multiplicity of resistance genes that have been identified so far. Read the table with the understanding that not all resistance mechanisms are found in all species of bacteria; particular resistance determinants are found in particular bacteria. For example, resistance to macrolides is determined by different mechanisms in campylobacter compared with those in staphylococci. Useful reviews are available on the various mechanisms including: an overview of acquired resistance genes (Schwarz et al. 2017, van Hoek et al. 2011); efflux-mediated antibiotic resistance (Li et al. 2015); tetracycline mechanisms and resistance determinants (Nguyen et al. 2014, Roberts 2011); antibiotics targeting bacterial cell walls and cell membranes (Bush 2012); and fluoroquinolone resistance (Yanat et al. 2017, Jacoby et al. 2014, Pallo-Zimmerman et al. 2010, Fàbrega et al. 2009). Of particular concern is combined resistance to fluoroquinolones and cephalosporins and the emergence of global MDR strains such as *E.coli* ST131 (Mathers et al. 2015, Nicolas-Chanoine et al. 2014). Some 'old' antibiotics such as colistin, used in some countries to control *E coli* infections (Rhouma et al. 2016), have been retrieved to try to manage the emerging pan-resistant Gram-negative infections (Giske 2015, Theuretzbacher et al. 2015). However, the appearance in China of a colistin resistance mechanism, involving the *mcr-1* gene, has raised concerns about the efficacy of this drug in humans due to the emergence of resistance (Bialvaei & Samadi Kafil 2015, Catry et al. 2015, Liu et al. 2015). More recently, a novel *mcr* gene, called *mcr-2*, was identified in Belgium in porcine and bovine colistin-resistant *E. coli* that did not contain *mcr-1* (Al-Tawfiq et al. 2016, Xavier et al. 2016).

[1] bla: bla is a gene that encodes the enzyme beta-lactamase.

[2] KPC: *Klebsiella pneumoniae* carbapenamase*;* OXA: O*xacillinase;* IMP: *Imipenemase*; VIM: *Verona integron-encoded metallo-ß-lactamase.*

An important constraint on the use of multiple antibiotics from a single class is the phenomenon of cross-resistance—where genes encoding resistance to one antibiotic in a class have the capacity to encode resistance to all antibiotics in that class. Another issue is co-selection for resistance (Cantón & Ruiz-Garbajosa 2011). This occurs when multiple antibiotic resistance genes are located on a single plasmid or other mobile genetic element, so one of the co-located genes selects for resistance to all antibiotics on that plasmid or mobile genetic element. The converse situation is collateral sensitivity that occurs when an organism which has developed resistance to one drug displays increased sensitivity to a second antibiotic (Pál et al. 2015).

Table 1. Examples of some common resistance mechanisms (based on Davies and Davies, 2010)

Class	Examples of antibiotics	Target	Resistance mechanisms	Examples of genes
Tetracyclines	• Oxytetracycline • Chlortetracycline • Doxycycline	Ribosome	Efflux altered target, modification of antibiotic	*tet*, *otr* families
Polypeptide	• Bacitracin	Peptidoglycan synthesis	Efflux	*bcr*
Macrolides	• Erythromycin • Tylosin • Tilmicosin • Tulathromycin • Kitasamycin • Spiramycin	Ribosome	Altered target, hydrolysis, glycosylation, phosphorylation, efflux	*erm*, *ere*, *mph*, *mef*, *msr*, *cfr* families, 23S rRNA SNPs*
Streptogramin	• Virginiamycin	Ribosome	Altered target, efflux, inactivation	*erm*, *vga*, *lsa*, vga, *vgb*, *vat*, *cfr* families
Lincosamides	• Lincomycin • Clindamycin	Ribosome	Inactivation, altered target, efflux	*erm, msr , lsa, inu, vga, cfr* families*
Pleuromutilins	• Tiamulin • Valnemulin	Ribosome	Efflux, altered target	*vga, lsa, sal, cfr,* 23S rRNA SNPs*

Class	Examples of antibiotics	Target	Resistance mechanisms	Examples of genes
β-lactams	• Penicillin • Ampicillin • Amoxicillin • Amoxicillin-clavulanate • Cloxacillin • Cefuroxime • Cephalexin • Cephalonium • Ceftiofur • Cefovecin • Cefquinome	Peptidoglycan synthesis	Hydrolysis, altered target, efflux	*bla, mec, ade, mex, cme* families
Aminoglycosides	• Gentamicin • Neomycin • Spectinomycin • Apramycin • Framycetin	Ribosome	Inactivation, altered target, efflux	*aac, ant, aph* families, *rmt, arm, ade, spw, spd*
Phenicols	• Florfenicol • Chloramphenicol	Ribosome	Inactivation, efflux, altered target	*flo, cfr, cat, cml* families, *optr*
Fluoroquinolones	• Enrofloxacin • Marbofloxacin • Orbifloxacin • Ibafloxacin • Pradofloxacin	DNA replication	Inactivation, efflux, altered target	Mutations in *gyrA, parC, qnr, aac(6')-Ib-cr, oqx*
Sulphonamides	• Sulfamethoxazole	Folic acid synthesis	Altered target, efflux	*sul* family, *acr* family
Pyrimidines	• Trimethoprim	Folic acid synthesis	Altered target, efflux	*dhfr* family, *bpr-opc* family
Nitrofurans	• Nitrofurazone • Nitrofurantoin	DNA	Target modification, porin changes	*nfs, omp*
Cationic polypeptides	• Polymixin B • Colistin	Cell membrane	Altered target, efflux	*mgr, pmrAB* mutations

*SNPs – single nucleotide polymorphisms

2 MODERN HISTORY OF ANTIMICROBIAL RESISTANCE ASSOCIATED WITH ANIMALS

2.1 Antibiotic use in animals

Antibiotics are used in animals as antibiotic growth promotants, for prophylaxis and metaphylaxis and therapeutically.

Growth promotant use

Using antibiotics to promote growth in animals has raised the most concern about selection pressure for antibiotic resistance. This approach involves in-feed use of low (generally sub-therapeutic) concentrations of antimicrobials, some of which belong to classes containing antibiotics that are of critical importance to human medicine. However ionophores, as yet not associated with antimicrobial resistance to therapeutic antibiotics in either humans or animals, make up by far the greatest quantity of in-feed antimicrobials. They are used as coccidiostats and rumen microflora modifiers and have some Gram-positive activity and hence promote growth. Antibiotic growth promotants (AGPs) are fed to animals in medicated feeds for extended periods of time, even for the whole life of the animal. Thus the use of such AGPs creates an ideal environment for selection of antibiotic-resistant bacteria and the spread of resistance genes in the intestinal tract of treated animals (Roy Chowdhury et al. 2014). Selection of antibiotic-resistant strains at low antibiotic concentrations has been reviewed by Sandegren (2014). The mode of action of AGPs remains unclear but they appear to exert their effect by:

- causing lethal or sublethal damage to Gram-positive bacteria (particularly) including intestinal pathogens
- reducing the production of bacterial toxins
- reducing the amount of essential nutrients used by bacteria
- allowing increased synthesis of vitamins and other growth factors
- improving absorption of nutrients by reducing the thickness of the intestinal epithelium
- reducing mucosa cell epithelial turnover and intestinal motility (Hao et al. 2014, Shryock & Page 2013).

However, there is evidence that the growth response to AGPs is small in optimised production systems where there are high standards of hygiene and disease control (Laxminarayan et al. 2015), reflecting the view that AGPs may exert their effect by controlling some subclinical enteric diseases associated with poor animal husbandry. Quantifying the extent to which growth responses are attributable to changes in the gut microflora or the control of subclinical enteric diseases is difficult (Brown et al. 2017, Callaway et al. 2003). Recent molecular advances have enabled studies into the effect of antibiotics on the non-cultivable gut microbiome, revealing that antibiotics cause disturbances to the beneficial gut microbial community which may have long term effects on immune system development, nutrient absorption and protection from pathogens (Nobel et al. 2015, Schulfer & Blaser 2015, Holman & Chénier 2014, Looft et al. 2014).

Therapeutic use

Therapeutic use generally involves individual animal treatment for larger livestock but, for chickens particularly, treatment is through drinking water or medicated feed. One problem with this dosing route is ensuring that each animal receives an appropriate dose; in particular, sick animals which may lose their appetite. Nevertheless, there is significant use of medicated feeds to treat larger livestock (Apley et al. 2012, Love et al. 2011).

Prophylactic and metaphylactic use both commonly involve administering antibiotics by injection (for example in cattle practice) or adding antibiotics to animal feeds. The intention is to use the medicated feed only in the face of a potential disease outbreak or to protect animals exposed to an infectious disease, so the treatment is only required for a limited period of time. There are use controls indicated on labels, and these should be complied with. The concentration of antibiotics in the feed for therapeutic use is usually much higher than for AGP use.

2.2 A global perspective on antimicrobial resistance associated with animals

Antimicrobial resistance in *E. coli* isolates from pigs and chickens was reported by Smith (1967) but it was not until the Swann Committee in the UK published its report on the emergence of MDR *Salmonella* in humans identical to strains causing infections in calves (Swann 1969) that much attention was paid to antibiotic use and resistance in animals. The committee recommended antibiotics important to human medicine be removed from animal feeds stating that "permission to supply and use an antibiotic without prescription for adding to animal feed should be restricted to antibiotics which:

- are of economic value in livestock production under UK farming conditions
- have little or no application as therapeutic agents in man or animals
- will not impair the efficacy of a prescribed therapeutic antibiotic or antibiotics through the development of resistant strains of organisms."

The UK and some countries including Australia responded by removing antibiotics such as penicillin and tetracyclines from non-prescription stock feeds. Other countries, such as the USA, did not take any action. The Food and Drug Administration (FDA) did recommend restrictions on the use of these antibiotics in feeds but Congress overruled the FDA and referred the matter to the National Academy of Sciences. The Academy was sceptical that low-level antibiotic use could increase the transmission of bacterial drug resistance from animals to humans and recommended that no restrictive actions on antibiotics be taken (Feinman 1998). However researchers in the USA (Levy 1985, Levy 1978) had already demonstrated that strains of *E coli* from animals, including strains carrying antibiotic resistance genes, could be transmitted to humans.

In the 1970s and 1980s increasing antibiotic resistance was recognised in zoonotic enteric bacteria such as *Salmonella* and campylobacter, as was the emergence of MDR strains, particularly in *Salmonella* and *E.coli*, but apart from expressions of concern, little action was taken (Barton 2000, Fone & Barker 1994, Levy 1985, Linton 1984). In 1986 the Swedish government banned the use of AGPs (Commission on Antibacterial Feed Additives 1997) and when Sweden joined the EU in 1995 special approval was required from the EU to maintain this ban (Wierup 2001). There was a sudden change in attitude when in 1995 *van*A vancomycin-resistant *Enterococcus faecium* was found in pigs and poultry that had been fed avoparcin-medicated feed (Bager et al. 1997). As a result, avoparcin was banned in Denmark in 1995 and other European countries soon followed suit. Apart from avoparcin there were also concerns about virginiamycin and co-selection for resistance to the human streptogramin quinupristin-dalfopristin (Werner et al. 1998), as well as tylosin in selecting for macrolide resistance and co-selecting for avoparcin resistance (Butaye et al. 1999).

There followed much debate about the use of AGPs and many reports were published with some supporting a ban on their use and others suggesting there was insufficient information to act (Barton 2000). In 1996 the EU suspended the registration of avoparcin. In 1999 it suspended the use of tylosin, spiramycin, bacitracin and

virginiamycin as well. By 2006 no AGPs remained registered in the EU (European Commission 2005). However some have raised concerns about the ban, suggesting it had no effect on vancomycin resistance in enterococci but had adverse effects on animal health (Casewell et al. 2003) and no benefits to human health (Phillips 2007). Other studies indicated that removing AGPs resulted in a substantial decline in antibiotic use (Millet & Maertens 2011), had not increased the use of therapeutic antibiotics except in weaner pigs in Denmark (Grave et al. 2006) and had led to a decline in antibiotic resistance in enterococci isolated from animals and food (Wegener 2003). In the 1990s, after the EU decision to phase out the use of AGPs, Denmark led the way by instituting a full voluntary ban in 1998, making it compulsory in 2000. The impact of the ban was discussed at a workshop in 2010 (Cogliani et al. 2011) and the conclusion was that animal production continued to thrive in countries where a ban on AGPs was enforced. However some still advocate for the continued use of AGPs (Hao et al. 2014).

Concern about global food security and problems in providing animal protein to a growing world population have invigorated the debate (Van Boeckel et al. 2015, Lean 2013), with calls to develop non-antibiotic growth promotants (Aiking 2014). It is worth noting that antibiotic resistance in enterococci is still an issue with *van*B *E faecium* endemic in many hospitals around the world, including in Australia (*van*B-encoded resistance is associated with vancomycin use in hospitals, not use of glycopeptides in animal feeds as the *van*B gene has not yet been recovered from enterococci of animal origin). Prevalence of *van*A VRE has increased in some countries too (Agersø et al. 2014) and is found in wastewater (Kim et al. 2017, Roberts et al. 2016) which could lead to contamination of agricultural products and animals. Recently linezolid resistance encoded by the *optrA* genes has been reported in *E faecium* and *E faecalis* isolated from food animals and carcasses (Tamang et al. 2017). Thus antibiotic resistance in enterococci remains a significant human health challenge (Werner et al. 2013). Heavy metals in animal feeds also have the potential to select for resistance to antibiotics due to the co-location of resistance determinants—copper and zinc have both been incriminated (Yu et al. 2017, Yazdankhah et al. 2014) and the EU has now recommended banning zinc oxide in animal feeds. Tylosin has had an impact on macrolide resistance in the non-enteric organism *Streptococcus suis* (Palmieri et al. 2011); Aarestrup et al. (1998) suggested that using too much tylosin in pigs led to this problem.

Until quite recently the focus was almost entirely on AGPs and there was limited interest in antibiotics used therapeutically in animals, perhaps in the mistaken belief by some in the medical sector and the wider community that all antibiotics were used for growth promotion. However, attention soon turned to two classes of antimicrobials critical in human medicine, the fluoroquinolones and 3rd generation cephalosporins. Also, resistant animal pathogens with multi-resistance conjugative elements and multi-resistance genes, such as *cfr*, which encodes resistance to phenicols, lincosamides, oxazolidinones (such as linezolid), pleuromutilins and streptogramin A, were reported firstly in staphylococci of human and animal origin and other Gram-positive bacteria. But they were soon found in enterococci and animal isolates of Gram-negative bacteria such as *Proteus* and *E. coli* (Tamang et al. 2017, Shen et al. 2013). Currently carbapenemase-producing and colistin-resistant MDR Gram-negative bacteria have taken centre stage in discussions on antibiotic resistance as carbapenems and colistin are antibiotics of last resort for infections caused by MDR Gram-negative bacteria (Al-Tawfiq et al. 2017, Madec et al. 2017, Michael et al. 2015, Morrison & Rubin 2015, Schmiedel et al. 2014).

Enrofloxacin (a fluoroquinolone) was introduced in Europe and the USA in the late 1980s and resistance was first reported in veterinary isolates of *Salmonella* in the mid-1990s (Griggs et al. 1994). A study of campylobacter isolates from humans and poultry showed parallel increases in resistance to enrofloxacin from 0 to 11 per cent and 0 to 14 per cent respectively between 1982 and 1989 (Endtz et al. 1991). Subsequent studies have confirmed the use of fluoroquinolones in food-producing animals to be a significant factor in the emergence of resistance in human infections (Nelson et al. 2007, Moore et al. 2006). Plasmid-borne fluoroquinolone resistance has now been found in animal isolates (Yanat et al. 2017, de Jong et al. 2014, Yang et al. 2014b, Pallo-Zimmerman et al. 2010).

Ceftiofur, a 3rd generation cephalosporin, was introduced to the USA in 1998 and prior to that in Europe. Deshpande et al. (2000) demonstrated that ESBL-producing human strains of *E.coli* and *Klebsiella pneumoniae* were resistant to ceftiofur and that there was a high correlation between resistance to ceftriaxone (a human 3rd generation cephalosporin) and ceftiofur in these isolates. Resistance to ceftiofur was first detected in *Salmonella* isolates in Canada and the USA in the late 1990s (Allen & Poppe 2002, CDC 2002). It was recognised that ceftiofur-resistant animal isolates produced AmpC and ESBL enzymes (Barton 2014, Smet et al. 2008). In recent years the term ESCs has been applied to the ESBLs which inactivate 3rd and 4th generation cephalosporins.

Over the 2000s many papers were published indicating strong links between the emergence of ESBLs/ESCs and the use of ceftiofur (and cefquinome, which has been approved for use for some time in Europe but is not currently approved in the USA or Australia) in livestock. ESBL-producing bacteria are now recognised as a major challenge to human health and more than 1,300 enzymes are currently recognised (Bush 2013). While most attention is paid to ESCs it is important not to overlook AmpC β-lactamases (Jacoby 2009), which are particularly associated with ceftiofur. Further, during the 2000s there were several reports of ESC-producing E.*coli* and *Salmonella* from animals (Tyrrell et al. 2016, Trott 2013, Carattoli 2008) and by the end of the decade attention was also drawn to the potential for ESC-*E.coli* in livestock to cause human extra-intestinal infections, such as urinary tract infections. [See the systematic review by Lazarus et al. (2015), which identified poultry as the most likely source]. ESC-producing organisms have been found with increasing frequency in companion animals, including dogs and horses (Madec et al. 2017, Rubin & Pitout 2014, Shaheen et al. 2011). The escalation in the number of reports of ESC-resistant organisms may have been associated with the introduction onto the EU market of cefquinome, a 4th generation cephalosporin, for use in dairy cattle and horses.

It is important to note that ESC activity is not restricted to E.*coli* and *Salmonella* but has been reported in many *Enterobacteriaceae* including *Citrobacter* spp., *Klebsiella* pneumoniae, *Serratia* spp. and *Enterobacter cloacae* as well as non-*Enterobacteriaceae* such as *Acinetobacter*. These organisms have largely been ignored in veterinary testing because most of them are not regarded as animal pathogens. The potential for Acinetobacter *baumannii* isolates from livestock and companion animals to cause human infections has been investigated by Müller et al. (2014) so the role of animals in the dissemination of the non-*E.coli*/*Salmonella* MDR organisms is slowly being revealed. However, antibiotic-resistant bacteria/genes could also be transferred from humans to animals, as suggested by Abraham et al. (2014b) and Schultz et al. (2015) in studies of MDR Proteus spp. in humans and dogs.

A further concern is the extension of the ESC activity to *carbapenems*, a treatment of last resort for some human infections. Carbapenems are not registered for use in animals but resistance has been detected in livestock, seafood, horses and companion animals (Madec et al. 2017, Michael et al. 2015, Morrison & Rubin 2015, Guerra et al. 2014). According to researchers in Germany (Falgenhauer et al. 2017) the most likely cause for this is co-selection, though at first it was thought it might be the result of transfer from humans to animals or off-label or illegal use in animals. Most of the ESC-producing organisms are multi-drug resistant and there is also an increasing number of reports of livestock and companion animals with ESC-resistant determinants on mobile plasmids (Seiffert et al. 2013). Also worrying has been the discovery in animal isolates of plasmids carrying both fluoroquinolone-resistant and ESC-resistant determinants (Wasyl et al. 2015, Li et al. 2014a) and the emergence of pandemic strains of MDR organisms such as *E.coli* ST131 (Mathers et al. 2015, Platell et al. 2011).

While most attention has been paid to risks to human health from antibiotic resistance in livestock, companion animals including horses have also come under scrutiny. This follows the emergence of fluoroquinolone-resistant and ESC-producing and carbapenemase-producing coliforms, as well as methicillin-resistant *Staphylococcus*

aureus (MRSA) (Bogaerts et al. 2015, Michael et al. 2015, Ewers et al. 2014, Guerra et al. 2014, Walther et al. 2014, Lloyd 2007).

MRSA first emerged in the 1960s and became the most common nosocomial pathogen in hospital patients (Moellering 2012). Subsequently, strains emerged in the general community (Williamson et al. 2014). MRSA was not thought to be an issue in animals until quite recently when there were increasing reports of MRSA in dogs and horses (Loeffler & Lloyd 2010, Leonard & Markey 2008). Molecular and epidemiological studies indicated that the cat and dog isolates were identical with human healthcare isolates whereas the horse isolates usually belonged to a horse-adapted strain of human origin (Walther et al. 2009). The accepted view is that cats and dogs are colonised by human strains and could potentially be a reservoir for human reinfection but that the horse-adapted strain circulates in horses and between horses and their handlers. MRSA was uncommon in livestock species (Leonard & Markey 2008) but this changed when livestock-associated MRSA (LA-MRSA) emerged in pigs (Huijsdens et al. 2006, Voss et al. 2005). This strain of MRSA (ST398) then spread rapidly and in a few years had established itself in many countries in livestock, particularly pigs, cattle, poultry and horses (Graveland et al. 2011, Cuny et al. 2010). ST398 does not appear to colonise humans very readily, nor does colonisation persist. Close and persistent contact with colonised animals appears to be a requirement for human colonisation (Fluit 2012). ST 398 is usually multi-drug resistant (Kadlec et al. 2012) and there are suggestions that use of tetracycline or other antibiotics may have contributed to its emergence (Price et al.). More recently there have been suggestions that the use of zinc has co-selected for LA-MRSA, as the Zn resistance and *mec* genes are co-located (Slifierz et al. 2015). Other livestock-associated strains have now emerged, for example MRSA ST9 in South East Asia (Chuang & Huang 2014) and the USA (Sun et al. 2015).

A further challenge has been the emergence in dogs and cats of methicillin-resistant *Staphylococcus pseudintermedius* (MRSP), first reported in 2011 (Beever et al. 2014, Moodley et al. 2014). To some extent this reflects the continuing evolution of methicillin resistance in staphylococci. It is significant that the emergence of MRSA in humans drove the introduction of vancomycin to treat resistant staphylococcal infections and this in turn led to the emergence of VRE.

In contrast to other food-producing animal industries there has been little interest in antibiotic resistance in aquaculture industries. Reilly and Käferstein (1999) drew attention to the potential for transfer of resistant bacteria from aquatic foodstuff to humans, noting in particular the widespread use of antibiotics in aquaculture in some Asian countries. In the last 10 to 15 years aquaculture has grown rapidly in many developed and developing countries, including Australia where it is worth $350 million a year, and the growth rate is likely to increase as wild-caught fishery stocks become depleted (FAO 2010). Although some aquaculture industries have invested heavily in vaccine development (Gudding R & Van Muiswinkel 2013) antibiotics are used extensively and in large volumes in other aquaculture industries (Park et al. 2012, Cabello 2006) and at least in some countries a high proportion of the antibiotics used are of critical importance in human medicine (Done et al. 2015). Widespread multi-drug resistance associated with plasmids and other mobile genetic elements has been found in aquaculture settings (Cabello et al. 2013, Miranda et al. 2013, Buschmann et al. 2012).

It may not be widely known but antibiotics have been used to control bacterial diseases in plants since the 1950s (McManus et al. 2002). The range of antibiotics is restricted (commonly streptomycin, gentamicin, oxytetracycline or oxolinic acid) and use is small compared to use in animal industries (Stockwell & Duffy 2012). However, these authors have noted that resistance to these antibiotics has been found in plant pathogenic bacteria.

Use of antibiotics in all settings has led to environmental contamination (da Costa et al. 2013). Human sewage (Bouki et al. 2015, Reinthaler et al. 2013), livestock production (Li et al. 2014b, Yang et al. 2014a, Novais et al.

2013, Zhang et al. 2013, Allen et al. 2011), and aquaculture (Hoa et al. 2011) have all contributed to widespread distribution of antibiotic-resistant bacteria and genes in the environment (Abhirosh et al. 2011, Heuer et al. 2011, Kümmerer 2009, Esiobu et al. 2002) facilitating their transmission to humans and animals (Wooldridge 2012, Young 1993).

2.3 The Australian situation

In many ways the situation in Australia is different to that overseas. This will be addressed later in this report. For now it is worth noting that in Australia the use of gentamicin is prohibited, fluoroquinolone use in food-producing animals has never been approved, use of 3rd generation cephalosporins is restricted and cefquinome has not been registered. MDR strains and important pathogens not present in Australian animals include: pathogenic MDR *Salmonella* Enteritidis, *Salmonella* Typhimurium DT104, *vanA* and *vanB* vancomycin-resistant enterococci (VRE) and fluoroquinolone-resistant Campylobacter spp. (Page 2012). However, while there is no national surveillance program, there is limited data on antimicrobial resistance available from some small pilot and snapshot studies.

Growth promotants have been used extensively in livestock and *vanA* enterococci were present in Australian poultry (Barton & Wilkins 2001) before avoparcin was withdrawn from the market in 2000. Resistance to bacitracin and tylosin is common in enterococci from poultry but little or no resistance to virginiamycin has been detected (Obeng et al. 2013, DAFF 2007). In pigs, there is widespread resistance to tylosin and bacitracin (Fard et al. 2011, Hart et al. 2004) and some resistance to virginiamycin (Fard et al. 2011). No vanA vancomycin resistance, even in isolates collected prior to 2000, has been reported. Interestingly, the pig industry voluntarily stopped using avoparcin in 1997. Fard et al. (2011) also noted that zinc resistance was common in E. *faecalis* but these workers did not detect any copper resistance. The only information on antibiotic resistance in enterococci from cattle comes from a small pilot surveillance study (DAFF 2007) which found low levels of resistance to virginiamycin and erythromycin (tylosin was not tested).

Multi-drug resistance has been reported in *Salmonella* from livestock (Izzo et al. 2011, Barton et al. 2003) with most isolations from pigs and poultry, though the prevalence of resistance in extensively grazed cattle is low (Barlow et al. 2015). Interestingly, the major multi-drug resistant strains such as *Salmonella* Typhimurium DT104, *Salmonella* Newport, *Salmonella* Heidelberg and *Salmonella* Kentucky have never been isolated from livestock and there are no reports of fluoroquinolone or 3rd generation cephalosporin resistance. Multi-drug resistant *E.coli* are much more common, again particularly in pigs and poultry (Abraham et al. 2014a, Obeng et al. 2012a, Smith et al. 2010, DAFF 2007, Hart et al. 2004, Barton & Wilkins 2001). *E.coli*-carrying integrons were reported in cattle (Barlow et al. 2008) and other studies have reported low levels of resistance in cattle (Barlow et al. 2015, DAFF 2007). Multi-drug fluoroquinolone-resistant *E.coli* have been isolated from extra-intestinal tract infections in dogs (Gibson et al. 2010) but none in livestock. Notably, Ingram et al. (2013) detected fluoroquinolone resistance in some samples of poultry meat despite the birds not being treated with fluoroquinolones. They concluded this arose because of co-selection as the isolates were also resistant to amoxicillin, gentamicin, tetracycline and trimethoprim/sulfamethoxazole and the apparent resistance determinant was aac(6')-Ib-cr, an aminoglycoside acetylating enzyme which also inactivates fluoroquinolones.

Recent investigations indicate that 3rd generation cephalosporin resistance is emerging in pig isolates (Shewli Mukerjee, Sam Abraham and Mary Barton, unpublished data) and calves (Sparham 2015) and has been found in pork and chicken meat (Pitcher et al. 2014). Postharvest contamination has not been ruled out in the latter case. Both fluoroquinolone and 3rd generation cephalosporin-resistant coliforms and *E.coli* have been found in dogs (Sidjabat et al. 2007) while IMP-carbapenemase has recently been detected in cats from a Sydney cattery (Abraham et al. 2016). Antibiotic-resistant strains of campylobacter have been found in Australian pigs and poultry

(Obeng et al. 2012b, Miflin et al. 2007, Hart et al. 2004, Barton & Wilkins 2001). There was also resistance to ampicillin and tetracycline but no resistance to fluoroquinolones was detected. Macrolide resistance in C. *jejuni*, which causes most human campylobacteriosis, generally remains low (Bolinger & Kathariou 2017) but increasing rates of resistance have been reported in US feedlot cattle (Tang et al. 2017).

In Australia multi-resistant MRSA has been found in dogs and cats (Allen et al. 2013, Malik et al. 2006) and horses (Allen et al. 2013, Axon et al. 2011). All small animal isolates have been ST239 and all horse isolates ST8 in keeping with overseas results. Large animal MRSA ST398 has recently been found in pigs (Groves et al. 2014) but there have been no reports of MRSA in bovine mastitis isolates (McMillan et al. 2016, Babra et al. 2013). The last published investigation of staphylococci in chickens reported finding no MRSA (Bertolatti et al. 2003). It is worth noting that Australian veterinarians in equine practice have MRSA carriage 23 times higher than in the general community (Jordan et al. 2011).

No antibiotics are registered for use in aquaculture in Australia but from time to time the APVMA has issued minor use permits (Barton & Ndi 2012). However, limited studies have indicated that antibiotic resistance is now common in Australian aquaculture isolates (Ndi & Barton 2011, Akinbowale et al. 2007a, Akinbowale et al. 2007b, Akinbowale et al. 2006).

3 ANTIBIOTIC SUSCEPTIBILITY TESTING

Antibiotic susceptibility testing is a well-established procedure in medical and veterinary diagnostic laboratories. It is a key assay both in helping determine the best antibiotic to use to treat a human or animal patient and in antibiotic resistance surveillance programs. It is essential to follow standardised procedures to ensure results are repeatable and that results from one laboratory are comparable to those from another for the compilation of common data. Susceptibility testing can involve phenotypic testing (ie determining the growth response of the organism of concern when exposed to the antibiotic) and genotypic testing (using polymerase chain reaction [PCR] to detect antimicrobial resistance genes of interest or whole genome and plasmid sequencing to detect the presence of antimicrobial resistance genes).

3.1 Phenotypic antibiotic susceptibility testing

Phenotypic testing can involve disc diffusion methods or broth or agar dilution methods. The former is the simplest and most commonly used technique in Australian veterinary laboratories. Two standardised methodologies are used—the Clinical Laboratory Standards Institute (CLSI) method and the Calibrated Dichotomous Sensitivity (CDS) method. CLSI methodology is internationally recognised and the Institute publishes a number of standard methodologies and interpretive guidelines, including some specifically for aquatic as well as veterinary isolates (CLSI 2014a, CLSI 2014b, CLSI 2013). CDS is restricted to Australia, has a medical focus and has only been calibrated for a few veterinary antibiotics. The Standing Committee on Animal Health Laboratory Standards (SCAHLS) has published standard testing procedures for Australian veterinary laboratories (SCAHLS 2014); this manual discusses the methods in detail. Disc diffusion methods use filter paper discs impregnated with specific concentrations of antibiotics. The diameter of the zone of inhibition of growth is measured and the size compared to those in tables in the CLSI guidelines. More information can be obtained by individually testing the susceptibility of the organism to a range of concentrations of the antibiotics of interest. This can be done manually for broth and agar dilution methods in smaller laboratories and automated systems are available for larger laboratories. Results are interpreted by determining the lowest concentration of antibiotic that inhibits the growth of the organism.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is another international body setting standards for antibiotic susceptibility. It is a standing committee jointly organized by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the European Centre of Disease Prevention and Control (ECDC) and European national breakpoint committees. It was formed in 1997 to harmonise susceptibility testing of human isolates in Europe; other countries including Australia are moving to this methodology.

Determining breakpoints (ie determining if an isolate is sensitive, intermediate or resistant) is a key step in clinical antibiotic susceptibility testing. Traditionally those following CLSI standards have used clinical breakpoints where an organism is considered susceptible if the zone diameter or minimum inhibitory concentration (MIC) is such that the antibacterial activity is associated with a high likelihood of therapeutic success. Conversely, a microorganism is defined as resistant if zone diameter or MIC are such that the level of antimicrobial activity is associated with a high likelihood of therapeutic failure—that is, the interpretations are based on potential clinical outcomes. EUCAST introduced the concept of microbiological resistance such that the breakpoints (more accurately cut-off values) are defined by epidemiological cut-off values (ECVs or ECOFF) (Silley 2012). The ECVs are established on the basis of the distribution of MICs for an antibacterial drug and a bacterial species. ECVs are much more applicable to surveillance testing than are clinical breakpoints (Bywater et al. 2006) and in epidemiological studies it is suggested that the terms ‘wild-type’ and ‘non-wild-type’ be used instead of the terms ‘susceptible’ and ‘resistant’ (Simjee et al. 2008). Both EUCAST and CLSI have robust methodologies for establishing breakpoints and ECVs,

though EUCAST is still establishing ECVs for veterinary medicines. The comparative functionality of EUCAST and CLSI with respect to methodologies and operational transparency is still debated although EUCAST has significant advantages for surveillance testing.

Another concept in clinical antibiotic susceptibility testing is the mutant selection window hypothesis (Drlica & Zhao 2007, Dong et al. 1999). This hypothesis states that antibiotic-resistant mutant subpopulations of bacteria present before starting antibiotic treatment are enriched and amplified during treatment when the concentration of the antibiotic is within a specific range (the mutant selection window). The lower margin of the window is the MIC of the susceptible organisms while the upper margin is the MIC of the least antibiotic-susceptible mutant subpopulation, a value called the mutant prevention concentration (MPC). The window is dependent on the pharmacokinetics of the antibiotic and concentration gradients in the body. Using a strategy based on the combined knowledge of MPC and pharmacokinetics and pharmacodynamics can reduce selection of resistant mutants (Cantón & Morosini 2011).

3.2 Molecular testing for antibiotic resistance

Molecular testing has been used for many years to identify the genes encoding resistance to antibiotics (Nikaido 2009). Some of the advantages and disadvantages have been discussed by Sundsfjord et al. (2004) who pointed out that the advantages of genotypic detection of resistance included speed and easy interpretation. Molecular methods also allow a better understanding of the mechanisms of resistance, such as the complex gene cassette required to encode glycopeptide resistance (Arthur & Courvalin 1993), the variant *mec* genes encoding methicillin resistance (Shore & Coleman 2013) or the 1300 plus *bla* genes encoding β-lactamase enzymes (Bush 2013). There are many genotyping techniques now available, from PCR to resistance gene sequencing and whole organism sequencing. Such methods facilitate ecological (Roy Chowdhury et al. 2014) and epidemiological investigations (Michael et al. 2015) and have led to a better understanding of the (two-way) transfer between animals and humans of antibiotic-resistant organisms and genes (Lupindu et al. 2015, Meireles et al. 2015, de Been et al. 2014, Harrison et al. 2014, Valentin et al. 2014, Wang et al. 2012, Wegener 2012). However, molecular techniques have limitations; the presence of a gene does not mean it will be expressed and gene variants may not be detected with standard primers.

4 GOVERNMENT AND AGENCY RESPONSES TO ANTIMICROBIAL RESISTANCE

4.1 International

The WHO was the first international agency to address antimicrobial resistance following a resolution from the 1998 World Health Assembly. It subsequently held a number of workshops and meetings to assess the perceived growing public health threat and to develop strategies for action; some of the consultations addressed issues arising from the use of antibiotics in animals (Stohr 2000). The WHO Global Strategy for Containment of Antimicrobial Resistance was published in 2001 (WHO 2001). At this time the WHO identified antimicrobial resistance as a key health issue for the 21st Century. Over the last 17 years it has continued to hold workshops and consultations, producing reports and guidelines on issues such as antimicrobial use and resistance surveillance, as well as specific guidance on the treatment of human infections (WHO 2015b). In May 2015 it released a global action plan on antimicrobial resistance (WHO 2015a).

The WHO (2001) report largely addressed antimicrobial resistance as it relates to the use of antimicrobials in human health but it also contained a chapter devoted to using antimicrobials in food-producing animals, which had been developed from a consultation (WHO 2000) with various veterinary organisations and individuals. The WHO report expressed concerns about, among other things:

- the large quantities of antimicrobials used for prophylaxis or growth promotion
- the lack of diagnostic services and their perceived high costs, meaning that treatment of animals is empiric rather than based on laboratory-proven disease
- the fact that veterinarians in some countries earn a significant proportion of their income from selling drugs—a disincentive to limit antimicrobial use
- inadequately enforced regulatory mechanisms
- antimicrobials used as growth promoters are often not considered as drugs so are either not licensed or licensed solely as feed additives and available over-the-counter with no professional intervention from veterinarians.

The report then discusses how the banning of avoparcin in Denmark led to a reduction of VRE in animals and a review of the use of AGPs. The issue of fluoroquinolone resistance in the zoonotic enteric pathogens *Salmonella* and campylobacter was also considered. A number of subsequent WHO publications also addressed antimicrobial resistance in food-producing animals (WHO 2015a, WHO 2002).

The World Organisation for Animal Health (OIE) responded by convening an ad hoc Group of Antimicrobial Resistance in 2003 (OIE 2015c) which updated some of the animal health codes to include antimicrobial resistance as well as some prudent use guidelines (OIE 2015a, Teale & Mouin 2012). It subsequently developed a list of antimicrobials critically important for animal use. This ranked a number of critically important human antibiotics such as fluoroquinolones and 3rd generation cephalosporins as also critically important in animal health. This list was updated in 2007 and again in 2015 (OIE 2015b); however, the status of fluoroquinolones or 3rd generation cephalosporins was not amended.

The FAO first addressed the issue of antimicrobial use in animals in the early 1980s in a joint FAO/WHO Expert Consultation on Residues of Veterinary Drugs in Food (FAO 1985). This consultation also recognised that

antibiotic-resistant organisms were associated with the use of sub-therapeutic concentrations of antibiotics in animal feeds and that the issue could need further consideration by FAO, WHO and other international agencies (Bruno & Mackay 2012). Much of the FAO work has been through Codex activities. In the early 2000s Codex collaborated with the WHO in two workshops to investigate a multi-disciplinary approach to coordinate activities and in 2005 published a code to minimise antimicrobial resistance (CAC 2005). In 2007 Codex established a Codex Intergovernmental Task Force on Antimicrobial Resistance. The role of the task force was to develop evidence-based guidelines to assess risks to human health associated with the emergence of antibiotic-resistant bacteria in animals and transmission via the food chain to humans. The task force prepared guidelines on risk analysis for food-borne transmission of resistance (CAC 2011). The key features of risk analysis, as part of an overall risk assessment, are: identify the hazard, decide who might be harmed by association and how, evaluate the risks and decide on control measures, record the findings and finally, review the assessment and update it if necessary. FAO is now actively engaged in working with a range of stakeholders, including national governments, producers and traders, on strategies to reduce antimicrobial use in livestock (including aquaculture) and prevent and control antimicrobial resistance (FAO 2015).

4.2 Australia

Current situation

An application submitted to the APVMA to register an antibiotic for use in animals requires a comprehensive data package which is subjected to a rigorous assessment. The following outline highlights the focal areas of the APVMA's antimicrobial resistance risk assessment; details of the data requirements are at apvma.gov.au/node/1018 (APVMA 2014b).

Applications submitted to register an antibiotic for use in food-producing animals require a qualitative risk assessment which addresses the possible contribution of the proposed use pattern to antibiotic resistance in foodborne microorganisms and human pathogens. In addition, a risk profile is required which summarises: hazard characterisation; exposure characterisation; impact characterisation; an assessment of the uncertainty of the data used in the risk assessment; the benefits of use of the antibiotic in Australian animal health and risk characterisation. In the context of AMR, a risk characterisation states the probability of disease due to infection in susceptible humans after exposure to antibiotic-resistant microorganisms (or transferable genetic elements) of animal origin and the severity of the impact of exposure on susceptible humans.

Similarly, an application to register an antibiotic for use in non-food-producing animals should include a qualitative risk assessment addressing risks associated with the potential transfer of antimicrobial-resistant bacteria (or their genetic material) from non-food-producing animals to humans. Where available, overseas data, Australian data, or both should also be submitted to the APVMA for assessment. The objective of this approach is to lessen the risk of antibiotic resistance further developing in bacterial populations and to ensure that the estimated level of risk is acceptable for public health. An approach similar to this one which has been practised in Australia for many years was recently proposed in the literature for evaluating new antimicrobial products for companion animals (Pomba et al. 2017).

Historical account

Initially, the National Health and Medical Research Council (NHMRC) was responsible for the national policy on antibiotics through its Antibiotic Standing Committee, which in 1988 was redesignated as the Expert Panel on

Antibiotics (EPA), and later renamed as the Working Party on Antibiotics (WPA)[3] . The guiding principles for the EPA/WPA were those outlined in the UK's Swann report. Special data requirements for registration were established and used by the then National Registration Authority (NRA)[4] (NRA 1998). The EPA/WPA provided advice to the NRA on whether to grant, refuse, restrict or amend an application and also advised the then Australia New Zealand Food Authority (ANZFA)[5] on the potential for an antibiotic used in animals to affect human pathogens. In response to WPA advice fluoroquinolones were never registered for use in food-producing animals. The lack of use in livestock combined with restricted use in humans combined to result in negligible resistance to fluoroquinolones in human enteric bacteria, in contrast to countries where fluoroquinolones are widely used in livestock and humans (Cheng et al. 2012).

Following the discovery in Denmark in 1995 of the link between the emergence of human VRE and use of avoparcin in animal feeds, in December 1997 the Australian Government established a Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR).

JETACAR was charged with:

- examining the status of antibiotic resistance patterns in Australia in human and veterinary practice and in food-producing animals
- examining the full range of antibiotic usage patterns and control practices in Australia in all sectors, including health, veterinary and agricultural applications
- identifying priority medical problems arising from the use of antibiotics in livestock production
- recommending a minimum set of criteria for assessing the potential human health impact prior to licensing of antibiotics for use in animals and agriculture, taking into account the likely benefits and potential adverse outcomes (informed by models in published scientific literature and relevant measures adopted by other countries)
- recommending an antibiotic resistance management strategy/strategies (JETACAR 1999).

JETACAR made 22 recommendations covering regulation, monitoring and surveillance, infection control, education and research and indicated that all five elements needed to be addressed if there was to be any impact

[3] The NHMRC made post-Swann recommendations on AGPs and scheduling at its 83rd meeting in 1977: **Antibiotics used as growth promotants in animal feedstuffs.** Council was of the opinion that the continued use of therapeutic antibiotics as growth promotants in animal feedstuffs could lead to an impairment of their efficacy in the treatment of human disease. Council recommended that penicillins, tetracyclines, cephlasporins, sulphonamides, trimethoprin and related compounds, aminoglycoside antibiotics, chloramphenicol, and preparations of these antibiotics, be prohibited from use as growth promotants in animal husbandry in Australia. It further considered that the use of tylosin and macrolides as growth promotants should continue to be permitted. However, the Council emphasised that it considered that their use as growth promotants is considered to be disadvantageous because of their value to veterinary medicine in the therapeutic treatment of serious infections in animals and birds.

[4] The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) was established in 1993 and underwent a name change to the Australian Pesticides and Veterinary Medicines Authority (APVMA) in 2003.

[5] The Australia New Zealand Food Authority (ANZFA) was established in 1996 as a successor to the National Food Authority (NFA) which was created in 1991. After further legislative change, the renamed Food Standards Australia New Zealand (FSANZ) was established in 2002.

on antibiotic resistance (JETACAR 2000). The government largely supported the recommendations (Department of Health and Ageing 2000) but most were not implemented. An Expert Advisory Group on Antimicrobial Resistance (EAGAR) was appointed to replace the WPA and continued to provide advice to the APVMA. EAGAR and the APVMA revised and updated the special data requirements for registration of veterinary antibiotics but EAGAR was disbanded in 2006 because the NHMRC did not consider it had a role in providing advice to the APVMA. Work on resistance in animals then stalled, apart from the voluntary removal of avoparcin from the market in 2000 and the review into virginiamycin which, although appealed, resulted in tighter controls on its use (APVMA 2004). There was also a small pilot antimicrobial resistance surveillance study (DAFF 2007) and most remaining non-prescription antibiotics were made prescription-only S4 drugs. In 2012 the Australian Commission on Safety and Quality in Health Care (ACSQHC) established an Antimicrobial Resistance Standing Committee (AMRSC). Among other things this group prepared a report titled *National surveillance and reporting of antimicrobial resistance and antibiotic usage for human health in Australia* (AMRSC 2013) and revised the previous EAGAR list of antibiotics critically important to human medicine (ACSQHC 2015).

In 2013, due to rising global concerns about antimicrobial resistance (World Economic Forum 2013) and noting the initiatives being taken internationally, a Senate committee investigated progress in implementing JETACAR's recommendations and made recommendations of its own (Finance and Public References Committee 2013). This led to greater consideration of resistance issues in both the human and animal sectors. AMRSC morphed into the Australian Strategic Technical Advisory Group on Antimicrobial Resistance (ASTAG) and is addressing use and resistance issues in animals and humans. In 2015 it released Australia's first national antimicrobial resistance strategy (Department of Health 2015). Now ASTAG is working to implement the strategy. Also in 2013 the Australian Government set up the Australian Antimicrobial Resistance Prevention and Containment Steering Group (AMRPC). Jointly chaired by the Secretaries of the Department of Health and the then Department of Agriculture, Fisheries and Forestry and with the Commonwealth Chief Medical Officer and Chief Veterinary Officer as senior members, the group's role is to provide high-level governance and leadership on AMR. It also oversees the development of a comprehensive National AMR Prevention and Containment Strategy for Australia. A successful AMR strategy will depend on collaboration not just across states but sectors.

A national One Health colloquium (ACSQHC 2013) recommended that a successful AMR strategy would depend on cross-sectoral collaboration. Key elements of effective cross-sectoral collaboration being:

- political will and high-level commitment
- common objectives and priorities
- shared benefits
- trust (transparency, communication and relationship building)
- adequate and equitably distributed resources
- identification and involvement of all relevant partners
- coordinated planning of activities
- capacity development.

The Australian Government announced in November 2016 the Implementation Plan of the National Antimicrobial Resistance Strategy 2015-2019 (Department of Health 2016).

5 MITIGATION OF ANTIBIOTIC RESISTANCE

Antimicrobial stewardship is well established in hospitals in many countries (Doron & Davidson 2011) including the Australian Commission on Safety and Quality in Health Care (ACSQHC 2015). As early as 2001 antimicrobial stewardship was seen as a key issue for veterinary use of antibiotics (Anthony et al. 2001) but progress in this area has not been as fast as might have been hoped. Programs are at various stages of implementation in Europe, the USA and Canada (AVMA Task Force for Antimicrobial Stewardship in Companion Animal Practice 2015, Bowen 2013, Fairles 2013). The Australian Veterinary Association is also actively engaged (Australian Veterinary Association 2014). Regulatory controls underpin any initiatives to reduce antibiotic resistance. In Australia there are three levels of control of antibiotic use in animals. Firstly, as no antibiotics are manufactured in Australia, there are customs controls at the point of entry. Secondly, all antimicrobials for use in animals must be registered by the APVMA. Thirdly, there is control-of-use legislation in each of the Australian states and territories. The registration process in Australia has been conservative and from 1970 to 2006 there was formal input from EAGAR and its predecessors as to the human health implications of introducing new classes of veterinary antibiotics for use in food-producing animals. As a result fluoroquinolones have not been registered for use in livestock, although a number of fluoroquinolones have been registered for therapeutic use in non-food-producing animals (dogs and cats). The initial approval to use cephalosporins in livestock was restricted but, in the change-over from the WPA to EAGAR, ceftiofur was registered for use in cattle, albeit with some label constraints.

One outcome from the implementation of JETACAR's recommendations has been the progressive removal of growth-promotant claims from antibiotics in classes important to human medicine. As a result the only growth-promotant antibiotics still registered in Australia are ionophores, kitasamycin, flavophospholipol, avilamycin and roxarsone. The states regulate the use of antibiotics and one of JETACAR's recommendations was to harmonise state legislation but this has yet to reach a satisfactory conclusion.

In 2015 the European Commission (EC) issued new guidelines to member states for the prudent use of antimicrobials in veterinary medicine. Critically, to mitigate the development of AMR, antimicrobials used in both humans and animals should only be used in animals in exceptional cases. The guidelines stress the need for cooperation between public health agencies, feed business operators, pharmaceutical manufacturers, veterinary and environmental authorities, industry bodies, front line veterinarians and farmers, all of whom have a responsibility in this area. But the EC said primary responsibility for prudent use, and thus mitigation of antimicrobial resistance, lies with the prescriber and the person administering the antimicrobials—ultimately the veterinarian familiar with the history of the herd, flock or animal being treated.

In the USA the US National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) was established in 1996 to oversee collaboration among state and local public health departments, the Centers for Disease Control (CDC), the FDA, and the US Department of Agriculture (USDA). This national surveillance system tracks changes in the antimicrobial susceptibility of certain enteric bacteria found in ill people (CDC), retail meats (FDA), and food animals (USDA) in the USA. The NARMS program at the CDC provides information about emerging bacterial resistance, the ways in which resistance is spread, and how resistant infections differ from susceptible infections (CDC 2017). The FDA regulates antimicrobials. In recent years it has moved to control the use of antibiotics of critical importance in human medicine and has issued detailed guidance for industry on the judicious use of medically-important antimicrobial drugs in food-producing animals (FDA 2013, FDA 2012). The FDA appears to have paid most attention to the use of antibiotics as feed additives for growth-promotant and prophylactic/metaphylactic use and less to therapeutic use (FDA 2015). This followed an instruction from President Obama that the FDA needed to take steps to stop agricultural use of medically-important antibiotics for growth promotion purposes (Park 2014, FDA 2013, FDA 2012). In May 2016 the FDA issued a rule expanding its

requirements for antimicrobial drug sponsors to provide data on a species-by-species basis for all antimicrobials sold or distributed for use in food-producing animals (FDA 2016). In line with its concerns about overuse of antimicrobials, in August 2016 the FDA banned 19 ingredients in antibacterial hand soap, including triclosan and triclocarban.

Globally there has been an increase in the level of political awareness of antibiotic resistance. For example, in 2013 the Chief Medical Officer of the UK, Dr Sally Davies, said antibiotic resistance was a "ticking time bomb" that posed a "catastrophic threat" (Davies 2015). In the same year the G8 Science Ministers identified AMR as the "major health security challenge of the 21st century" and promised to act on antibiotic resistance. As already mentioned, President Obama entered the debate in 2014 and set up a task force to come up with an action plan which it did in the same year (President's Council of Advisors on Science and Technology 2014). Political interest in antibiotic resistance has generated a substantial increase in funding, at least in the UK and USA, to address the resistance crisis.

Professional organisations also play an important role. For example the British Veterinary Association (BVA) and European veterinary organisations have over the years produced formularies and prudent use guidelines. The Australian Veterinary Association (AVA) has also been addressing the issue of antimicrobial resistance. It is one of five key strategic priorities for the AVA although a lack of funding is hampering efforts to prepare prudent-use guidelines. Some of the Special Interest Groups of the AVA have developed guidelines—for example, the Australian Veterinary Poultry Association has published several documents relating to the judicious use of antibiotics (AVPA 2013). The AVA and Animal Medicines Australia (AMA) have joined forces to develop best practice antibiotic-prescribing guidelines for livestock and horses (Animal Medicines Australia 2015). Individual practitioners are expected to use antibiotics responsibly, and in this respect the AVA invited small animal veterinary practices in Canberra to participate in a 12-month pilot trial that began in March 2016 (Australian Veterinary Association 2016).

While regulatory controls and antimicrobial stewardship programs should help in delaying the emergence of resistance to any new classes of antibiotics, it is far from clear what difference they will make to existing resistance problems. Evaluations of medical programs indicate there have been economic benefits in reducing the volume of antibiotics used in hospitals (Coulter et al. 2015); however, as yet, there are no published studies indicating any reduction in antibiotic resistance. The conventional wisdom has been that antibiotic resistance imposes such a cost on the organism that as soon as the selection pressure of antibiotic resistance is removed, resistant strains will rapidly be replaced by sensitive strains. However, in practice this does not seem to be the case (Melnyk et al. 2014, Andersson & Hughes 2010) or that if resistance is reversed, it probably happens quite slowly (Sundqvist 2014). Another level of intervention is educating the community in general, and livestock and pet owners in particular, to increase knowledge about when and how antibiotics should be used and, conversely, when their use is inappropriate. Medical, veterinary and animal science courses also need to pay serious attention to appropriate training on appropriate antibiotic use and the mitigation of antibiotic resistance.

History suggests that it takes a crisis to get any action on antibiotic resistance. First it was multi-drug resistance in *Salmonella* that stimulated the Swann (1969) report; then it was the discovery of the link between avoparcin use in animals and VRE that led to the WHO taking a more proactive stance. Now it is the emergence of pan-resistant organisms and ESCs that has increased government concerns and led to the latest development—recognition that antibiotic resistance is truly a One Health issue that will only be mitigated if medical and veterinary authorities work closely together on an international platform (Laxminarayan et al. 2015, The Lancet Infectious Diseases Commission 2013). This has added impetus to joint WHO/OIE and FAO collaborations.

6 CONCLUSION

Antibiotic resistance will not disappear but every effort must be made to delay its emergence and reduce its impact on human health and animal health, welfare and productivity. While protecting human health is essential, effective antibiotics are also needed to treat animals, including companion animals. However, it is prudent public health policy that the available armamentarium of veterinary antibiotics should not include those that are medically important. Appropriate and consistent regulations and industry stewardship programs are essential to ensure that veterinary antibiotics are used responsibly. This is also a food security issue. To increase food production in a sustainable way, alternatives to the widespread use in many countries of antibiotics as growth promotants need to be introduced. Among these, improved genetics, improved hygiene, and improved diets play a role. Also, the use of prophylactic antibiotics in animals must be managed responsibly to ensure health and welfare are maintained and antimicrobial resistance is not amplified.

While much of the research is on finding new antibiotics, it is also important to encourage research on how to change the way antibiotics are used. If newer antibiotics are not used prudently, resistance will emerge to them just as it has to every other antibiotic introduced into human and veterinary medicine. Improving antibiotic stewardship must go hand-in-hand with improved infection control (human and veterinary) and improved animal management and biosecurity on farms. The ASTAG Committee is seeking to develop a unified approach to regulating and managing antibiotic use in Australia; this will help to ensure progress in controlling the emergence of antibiotic resistance.

The Australian Government has a long-standing commitment to regulate and register agricultural and veterinary chemicals through the APVMA, which has become the principal authority managing AMR in animals. Andrew Metcalfe, former Secretary of the Department of Agriculture, Fisheries and Forestry (now the Department of Agriculture and Water Resources) told the Australian One Health Antimicrobial Resistance Colloquium in July 2013 that through the APVMA, Australia has one of the most thorough systems for regulating chemicals, including antibiotics, in the world. This country also has one of the lowest nonhuman uses of antibiotics in the world, and one of the lowest levels of AMR, but there is no room for complacency—humans and animals share many of the same bacteria and environments and AMR bacteria are able to move between species and environments across the world.

APPENDIXES

ABBREVIATIONS

ACSQHC	Australian Commission on Safety and Quality in Health Care
AGP	Antibiotic growth promotant
ABR	Antibiotic resistance
AMA	Animal Medicines Australia
AMR	Antimicrobial resistance
APVMA	Australian Pesticides and Veterinary Medicines Authority
ASTAG	Australian Strategic and Technical Advisory Committee on Antibiotic Resistance
AVA	Australian Veterinary Association
CAC	Codex Alimentarius Commission ('Codex')
CLSI	Clinical and Laboratory Standards Institute
EAGAR	Expert Advisory Group on Antimicrobial Resistance
ECOFF	epidemiological cut-off value
ECV	(see ECOFF)
ESBL	Extended spectrum β-lactamase
ESC	Extended spectrum cephalosporinase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	US Food and Drug Administration
FAO	Food and Agriculture Organization of the United Nations
FSANZ	Food Standards Australia New Zealand
JETACAR	Joint Expert Technical Advisory Committee on Antimicrobial Resistance
LA-MRSA	Livestock-associated MRSA (see MRSA)
MDR	Multidrug resistance
MRSA	Methicillin-resistant *Staphylococcus aureus*
NARMS	US National Antimicrobial Resistance Monitoring System for Enteric Bacteria
NHMRC	National Health and Medical Research Council
OIE	World Organisation for Animal Health

TGA	Therapeutic Goods Administration
USDA	US Department of Agriculture
VRE	Vancomycin-resistant Enterococcus
WHO	World Health Organization

GLOSSARY

Acquired resistance	Acquired resistance occurs when a particular microorganism obtains the ability to resist the activity of a particular antimicrobial agent to which it was previously susceptible. A bacterial strain can acquire resistance by mutation, by the uptake of exogenous genes by horizontal transfer from other bacterial strains or by the activation/triggering of a genetic cascade, thereby inducing the expression of resistance mechanisms (E. M. A. Committee for Medicinal Products for Veterinary Use et al. 2017).
Antibiotics	Originally defined as substances produced by microorganisms but now including synthetic substances that at low concentrations kill or inhibit the growth of other microorganisms but cause little or no host damage. They are drugs used to treat infections caused by bacteria, but not those caused by viruses, fungi or parasites. Antibiotic as used in this document is synonymous with antibacterial.
Antibiotic growth promoters/promotants (AGPs)	AGPs are reported to improve growth rates and production (meat, milk, eggs). Although the mechanism underpinning their action is unclear, one of many mechanisms is believed to be that sub-therapeutic doses of antibiotic growth promoters may suppress subclinical infections. The effects of growth promoters are more noticeable in at risk and/or sick animals and sometimes in those suffering from poor animal husbandry (Hughes & Heritage 2002).
Antibiotic resistance	A property of bacteria that enables them to grow in the presence of antibiotic concentrations that would normally kill or suppress the growth of susceptible bacteria (APVMA 2014a). Antimicrobial resistance (*see below*) is a broader term, encompassing resistance to drugs to treat infections caused by other microbes as well, such as parasites (eg malaria), viruses (eg HIV) and fungi (eg *Candida*).
Antimicrobials	An active substance of synthetic or natural origin which destroys microorganisms, suppresses their growth or their ability to reproduce after administration for therapeutic indications in animals or humans. In this context, antivirals, antiparasitics (eg coccidiostats) and disinfectants are excluded from the definition (EMA 2015). However the term 'antimicrobial' is often used interchangeably with 'antibiotic'.
Antimicrobial resistance	The inability or reduced ability of an antimicrobial agent to inhibit the growth of a bacterium which, in the case of a pathogenic organism, can lead to therapy failure (EFSA 2016).
Co-resistance	The presence of resistance genes located on the same piece of DNA encoding resistance to more than one class of antibiotics or other substances (for example heavy metals or disinfectants) in a single bacterium. This event often occurs on a mobile piece of DNA in the chromosome or on a plasmid (Baker-Austin et al. 2006).
Co-selection	The simultaneous selection of genes co-located with resistance genes that occurs when a single gene is selected by exposure to a single antibiotic or other selective substance. The classic example is integron-containing resistance gene cassettes under the control of a single promoter.
Cross resistance	Resistance to a particular antibiotic that often results in resistance to other antibiotics, usually from a similar chemical class, to which the bacteria may not have been exposed. A single resistance mechanism confers resistance to an entire class (or family) of antibiotics (Cantón & Ruiz-Garbajosa 2011). Cross resistance can also occur across different classes of antibiotics. This could be a result of either overlapping targets of the different antibiotics, as is the case with macrolides and lincosamides, or the bacteria having a similar resistance mechanism to the different compounds (E. M. A. Committee for Medicinal Products for Veterinary Use et al. 2017).

Intrinsic resistance	Some bacteria are naturally resistant to some classes of antibiotics because their structure prevents antibiotics getting into the bacterial cell, or their structures are not susceptible to the action of the antibiotic, or they have a natural ability to eliminate or destroy the antibiotic.
Metaphylaxis	Administering antimicrobial drugs to a group of animals judged to be clinically healthy but which are in contact with animals with clinical signs of infection.
Multidrug resistance (MDR)	MDR is defined as non-susceptibility to at least one agent in three or more antimicrobial categories (Magiorakos et al. 2012).
Prophylaxis	Administering antimicrobial drugs to a single healthy animal known to be at risk due to, for example, it being in close proximity to other animals, or stress caused by transport or adverse weather conditions.

USEFUL RESOURCES

Australian Veterinary Association (2014) Veterinary use of antibiotics critical to human health. http://www.ava.com.au/sites/default/files/AVA_website/pdfs/Veterinary%20use%20of%20antibiotics%20critical%20to%20human%20health.pdf

Australian Veterinary Association (2014) Developing a national antibiotic resistance strategy for Australia. http://www.ava.com.au/sites/default/files/AVA_website/pdfs/AVA%20AMR%20strategy%20discussion%20paper%20submission%20FINAL.pdf

Department of Agriculture (2015) Antimicrobial resistance. http://www.agriculture.gov.au/animal/health/amr

Department of Health, Antimicrobial Resistance Standing Committee (2014) AMRSC Importance ratings and summary of antibacterial uses in humans in Australia. http://www.health.gov.au/internet/main/publishing.nsf/Content/1803C433C71415CACA257C8400121B1F/$File/importance-ratings-summary-antimicrobial-uses-humans-Aust-july2014.pdf

Note that AMRSC has been replaced by the Australian Strategic and Technical Advisory Committee on Antibiotic Resistance (ASTAG) and the above list of importance ratings is under review.

Department of Health/Department of Agriculture (2015) Responding to the threat of antimicrobial resistance – Australia's first antimicrobial resistance strategy 2015-2019. http://www.health.gov.au/internet/main/publishing.nsf/Content/1803C433C71415CACA257C8400121B1F/$File/amr-strategy-2015-2019.pdf

FAO (2015) http://www.fao.org/antimicrobial-resistance/en/

Joint FAO/WHO/OIE/ expert meeting on critically important antimicrobials, Rome, 2007. ftp://ftp.fao.org/docrep/fao/010/i0204e/i0204e00.pdf

OIE (2015) Antimicrobial agents and antimicrobial resistance. http://www.oie.int/our-scientific-expertise/veterinary-products/antimicrobials/

OIE (2016) The OIE strategy on antimicrobial resistance and the prudent use of antimicrobials. http://www.oie.int/our-scientific-expertise/veterinary-products/antimicrobials/

WHO (2015) Antimicrobial resistance. http://www.who.int/mediacentre/factsheets/fs194/en/

REFERENCES

Aarestrup, F, Rasmussen, S, Artursson, K & Jensen, N 1998, 'Trends in the resistance to antimicrobial agents of Streptococcus suis isolates from Denmark and Sweden', *Vet Microbiol.*, vol. 63, pp. 71-80.

Abhirosh, C, Sherin, V, Thomas, A, Hatha, A & Mazumder, A 2011, 'Potential public health significance of faecal contamination and multidrug-resistant Escherichia coli and Salmonella serotypes in a lake in India', *Public Health*, vol. 125, pp. 377-379.

Abraham, S, Trott, D, Jordan, D, Gordon, D, Groves, M, Fairbrother, J, Smith, M, Zhang, R & Chapman, T 2014a, 'Phylogenetic and molecular insights into the evolution of multidrug-resistant porcine enterotoxigenic Escherichia coli in Australia', *Int J Antimicrob Agents*, vol. 44, pp. 105-111.

Abraham, S, Wong, H, Turnidge, J, Johnson, J & Trott, D 2014b, 'Carbapenemase-producing bacteria in companion animals: a public health concern on the horizon', *J Antimicrob Chemother*, vol. 69, pp. 1155-1557.

Abraham, S, O'Dea, M, Trott, DJ, Abraham, RJ, Hughes, D, Pang, S, McKew, G, Cheong, EYL, Merlino, J, Saputra, S, Malik, R & Gottlieb, T 2016, 'Isolation and plasmid characterization of carbapenemase (IMP-4) producing Salmonella enterica Typhimurium from cats', *Scientific Reports*, vol. 6, pp. 35527.

ACSQHC 2013, 'Australian One Health Antimicrobial Resistance Colloquium background paper', available at https://www.safetyandquality.gov.au/wp-content/uploads/2013/07/Briefing-paper-for-One-Health-AMR-Colloquium-participants-Final-Jul-2013.pdf.

---- 2015, 'Antimicrobial stewardship resource materials', available at http://www.safetyandquality.gov.au/our-work/healthcare-associated-infection/antimicrobial-stewardship/resource-materials/.

---- 2017, *Antimicrobial Resistance Standing Committee,* available at http://www.safetyandquality.gov.au/our-work/healthcare-associated-infection/antimicrobial-resistance-standing-committee/.

Agersø, Y, Bager, F, Boel, J, Dalby, T, Hammerum, A, Helwigh, B, Hoffmann, S, Høg, B, Jensen, L, de Knegt, L, Korsgaard, H, Kuhn, K, Larsen, A, Larsen, L, Laursen, M, Neilsen, E, Olsen, S, Petersen, A, Skjøt-Rasmussen, L, Skov, R, Slotved, H-C, Sørensen, A & Torpdahl, M 2014, *DANMAP 2013 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark*, DANMAP Copenhagen, available at http://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP%202013/DANMAP%202013.ashx.

Aiking, H 2014, 'Protein production: planet, profit, plus people?', *Am J Clin Nutr*, vol. 100, pp. 483S-489S.

Akinbowale, O, Peng, H & Barton, M 2006, 'Antimicrobial resistance in bacteria isolated from aquaculture sources in Australia', *J Appl Microbiol*, vol. 100, pp. 1103-1013.

---- 2007a, 'Diversity of tetracycline resistance genes in bacteria from aquaculture sources in Australia', *J Appl Microbiol*, vol. 103, pp. 2016-2025.

Akinbowale, O, Peng, H, Grant, P & Barton, M 2007b, 'Antibiotic and heavy metal resistance in motile aeromonads and pseudomonads from rainbow trout (Oncorhynchus mykiss) farms in Australia', *Int J Antimicrob Agents*, vol. 30, pp. 177-182.

Al-Tawfiq, JA, Laxminarayan, R & Mendelson, M 2016, 'How should we respond to the emergence of plasmid-mediated colistin resistance in humans and animals?', *Int J Infect Dis*, vol. 54, pp. 77-84.

---- 2017, 'How should we respond to the emergence of plasmid-mediated colistin resistance in humans and animals?', *Int J Infect Dis*, vol. 54, pp. 77-84.

Allen, J, Abraham, L, Thompson, K & Browning, G 2013, 'Methicillin-resistant Staphylococcus aureus: an issue for veterinary hospitals', *Aust Vet J,* vol. 91, pp. 215-219.

Allen, K & Poppe, C 2002, 'Occurrence and characterization of resistance to extended-spectrum cephalosporins mediated by beta-lactamase CMY-2 in Salmonella isolated from food-producing animals in Canada', *Can J Vet Res*, vol. 66, pp. 137-144.

Allen, S, Boerlin, P, Janecko, N, Lumsden, J, Barker, I, Pearl, D, Reid-Smith, R & Jardine, C 2011, 'Antimicrobial resistance in generic Escherichia coli isolates from wild small mammals living in swine farm, residential, landfill, and natural environments in southern Ontario, Canada', *Appl Environ Microbiol*, vol. 77, pp. 882-887.

AMRSC 2013, 'National surveillance and reporting of antimicrobial resistance and antibiotic usage for human health in Australia. Antimicrobial Resistance Standing Committee. June 2013', available at https://www.griffith.edu.au/__.../SAQ065_ProjectAMRAU_AHPPC_Approval.pdf.

Andersson, D & Hughes, D 2010, 'Antibiotic resistance and its cost: is it possible to reverse resistance? ', *Nat Rev Microbiol*, vol. 8, pp. 260-271.

Animal Medicines Australia 2015, *New prescribing guidelines for livestock and horses*, available at http://animalmedicinesaustralia.org.au/new-prescribing-guidelines-for-livestock-and-horses/.

Anthony, F, Acar, J, Franklin, A, Gupta, R, Nicholls, T, Tamura, Y, Thompson, S, Threlfall, E, Vose, D, van Vuuren, M, White, D & Office International des Epizooties Ad hoc Group 2001, 'Antimicrobial resistance: responsible and prudent use of antimicrobial agents in veterinary medicine', *Rev Sci Tech Off Int Epiz,* vol. 20, pp. 829-839.

Apley, M, Bush, E, Morrison, R, Singer, R & Snelson, H 2012, 'Use estimates of in-feed antimicrobials in swine production in the United States', *Foodborne Pathog Dis*, vol. 9, pp. 272-279.

APVMA 2004, 'The findings of the reconsideration of registration of products containing virginiamycin, and their labels', available at http://apvma.gov.au/sites/default/files/publication/14231-virginiamycin-final-review-report.pdf.

---- 2014a, *Antibiotic resistance*, available at http://apvma.gov.au/node/1013.

---- 2014b, *Antibiotic resistance risk assessments*, available at http://apvma.gov.au/node/1018.

Arthur, M & Courvalin, P 1993, 'Genetics and mechanisms of glycopeptide resistance in enterococci', *Antimicrob Agents Chemother*, vol. 37, pp. 1563-1571.

Australian Veterinary Association 2014, 'Fighting antimicrobial resistance', available at http://www.ava.com.au/amr.

---- 2016, *Pilot trial of an antimicrobial stewardship program in companion animal practice*, available at http://www.ava.com.au/ams.

AVMA Task Force for Antimicrobial Stewardship in Companion Animal Practice 2015, 'Antimicrobial stewardship in companion animal practice', *J Am Vet Med Assoc* vol. 246, pp. 287-288.

AVPA 2013, *Therapeutics - dose & restraints*, available at http://www.avpa.asn.au/support-for-the-veterinarian/therapeutics-dose-restraints/.

Axon, JE, Carrick, JB, Barton, MD, Collins, NM, Russell, CM, Kiehne, J & Coombs, G 2011, 'Methicillin-resistant Staphylococcus aureus in a population of horses in Australia', *Aust Vet J*, vol. 89, pp. 221-225, available at http://dx.doi.org/10.1111/j.1751-0813.2011.00711.x.

Babra, C, Tiwari, J, Pier, G, Thein, T, Sunagar, R, Sundareshan, S, Isloor, S, Hegde, N, de Wet, S, Deighton, M, Gibson, J, Costantino, P, Wetherall, J & Mukkur, T 2013, 'The persistence of biofilm-associated antibiotic resistance of Staphylococcus aureus isolated from clinical bovine mastitis cases in Australia', *Folia Microbiol (Praha)*, vol. 58, pp. 469-474.

Bae, J, Oh, E & Jeon, B 2014, 'Enhanced transmission of antibiotic resistance in Campylobacter jejuni biofilms by natural transformation', *Antimicrob Agents Chemother*, vol. 58, pp. 7573-7575.

Bager, F, Madsen, M, Christensen, J & Aarestrup, F 1997, 'Avoparcin used as a growth promoter is associated with the occurrence of vancomycin-resistant Enterococcus faecium on Danish poultry and pig farms', *Prev Vet Med*, vol. 31, pp. 85-112.

Baker-Austin, C, Wright, M, Stepanauskas, R & McArthur, J 2006, 'Co-selection of antibiotic and metal resistance', *Trends Microbiol*, vol. 14, pp. 176-82.

Balcazar, J 2014, 'Bacteriophages as vehicles for antibiotic resistance genes in the environment', *PLoS Pathog*, vol. 10, pp. e1004219.

Barlow, R, Fegan, N & Gobius, K 2008, 'A comparison of antibiotic resistance integrons in cattle from separate beef meat production systems at slaughter', *J Appl Microbiol*, vol. 104, pp. 651-658.

Barlow, R, McMillan, K, Duffy, L, Fegan, N, Jordan, D & Mellor, G 2015, 'Prevalence and antimicrobial resistance of Salmonella and Escherichia coli from Australian cattle populations at slaughter', *J Food Prot*, vol. 78, pp. 912-920.

Barton, M & Wilkins, J 2001, *Antibiotic resistance in bacteria isolated from poultry*, RIRDC project number USA-9A report number 01/105, RIRDC,

Barton, M, Pratt, R & Hart, W 2003, 'Antibiotic resistance in animals', *Commun Dis Intell Q Rep*, vol. 27, pp. S121-126.

Barton, M & Ndi, O 2012, 'Can we feel it in our waters? Antimicrobials in aquaculture', *Med J Aust*, vol. 197, pp. 487-488.

Barton, M 2014, 'Impact of antibiotic use in the swine industry', *Curr Opin Microbiol*, vol. 19, pp. 9-15.

Barton, MD 2000, 'Antibiotic use in animal feed and its impact on human health', *Nutrition Research Reviews*, 13, 279-299, available at https://www.cambridge.org/core/journals/nutrition-research-reviews/article/div-classtitleantibiotic-use-in-animal-feed-and-its-impact-on-human-healtdiv/1A4578D31BF22D355C561E8A4A1D1013.

Beever, L, Bond, R, Graham, P, Jackson, B, Lloyd, D & Loeffler, A 2014, 'Increasing antimicrobial resistance in clinical isolates of Staphylococcus intermedius group bacteria and emergence of MRSP in the UK', *Vet Rec*, vol. 176, pp. 172.

Bertolatti, D, O'Brien, F & Grubb, W 2003, 'Characterization of drug-resistant Staphylococcus aureus isolated from poultry processing plants in Western Australia', *Int J Environ Health Res*, vol. 1, pp. 43-54.

Bialvaei, A & Samadi Kafil, H 2015, 'Colistin, mechanisms and prevalence of resistance', *Curr Med Res Opin*, vol. 31, pp. 707-721.

Blair, J, Webber, M, Baylay, A, Ogbolu, D & Piddock, L 2015, 'Molecular mechanisms of antibiotic resistance', *Nat Rev Microbiol*, vol. 13, pp. 42-51.

Bogaerts, P, Huang, T, Bouchahrouf, W, Bauraing, C, Berhin, C, El Garch, F & Glupczynski, Y 2015, 'Characterization of ESBL- and AmpC-producing Enterobacteriaceae from diseased companion animals in Europe', *Microb Drug Resist*, available at http://online.liebertpub.com/doi/abs/10.1089/mdr.2014.0284.

Bolinger, H & Kathariou, S 2017, 'The current state of macrolide resistance in campylobacter: a review of trends and impacts of resistance mechanisms ', *Appl Environ Microbiol*, [Epub ahead of print], available at http://aem.asm.org/content/early/2017/04/10/AEM.00416-17.abstract.

Bouki, C, Venieri, D & Diamadopoulos, E 2015, 'Detection and fate of antibiotic resistant bacteria in wastewater treatment plants: a review', *Ecotoxicol Environ Saf*, vol. 91, pp. 1-9.

Bowen, M 2013, 'Antimicrobial stewardship: time for change', *Equine Vet J,* vol. 45, pp. 127-129.

Brown-Jaque, M, Calero-Cáceres, W & Muniesa, M 2015, 'Transfer of antibiotic-resistance genes via phage-related mobile elements', *Plasmid,* vol. 79, pp. 1-7.

Brown, K, Uwiera, RR, Kalmokoff, ML, Brooks, SP & Inglis, GD 2017, 'Antimicrobial growth promoter use in livestock: a requirement to understand their modes of action to develop effective alternatives', *Int J Antimicrobial Agents*, vol. 49, pp. 12-24.

Bruno, AV & Mackay, C 2012, 'Antimicrobial resistance and the activities of the Codex Alimentarius Commission', *Revue scientifique et technique (International Office of Epizootics)*, vol. 31, pp. 317-323, available at http://europepmc.org/abstract/MED/22849286.

Buschmann, A, Tomova, A, López, A, Maldonado, M, Henríquez, L, Ivanova, L, Moy, F, Godfrey, H & Cabello, F 2012, 'Salmon aquaculture and antimicrobial resistance in the marine environment', *PLoS One,* vol. 7, pp. e42724.

Bush, K 2012, 'Antimicrobial agents targeting bacterial cell walls and cell membranes', *Rev Sci. Tech*, vol. 31, pp. 43-56.

---- 2013, 'The ABCD's of β-lactamase nomenclature', *J Infect Chemother*, vol. 19, pp. 549-559.

Butaye, P, Devriese, L & Haesebrouck, F 1999, 'Phenotypic distinction in Enterococcus faecium and Enterococcus faecalis strains between susceptibility and resistance to growth-enhancing antibiotics', *Antimicrob Agents Chemother,* vol. 43, pp. 2569-2570.

Bywater, R, Silley, P & Simjee, S 2006, 'Antimicrobial breakpoints-definitions and conflicting requirements', *Vet Microbiol*, vol. 118, pp. 158-159.

Cabello, F 2006, 'Heavy use of prophylactic antibiotics in aquaculture: a growing problem for human and animal health and for the environment', *Environ Microbiol*, vol. 8, pp. 1137-1144.

Cabello, F, Godfrey, H, Tomova, A, Ivanova, L, Dölz, H, Millanao, A & Buschmann, A 2013, 'Antimicrobial use in aquaculture re-examined: its relevance to antimicrobial resistance and to animal and human health', *Environ Microbiol*, vol. 15, pp. 1917-1942.

CAC 2005, 'Code of practice to minimise and contain antimicrobial resistance. CAC/RCP 61-2005' in *Codex texts on antimicrobial resistance,* available at http://www.fao.org/3/a-i4296t.pdf.

---- 2011, 'Guidelines for risk analysis of foodborne antimicrobial resistance. CAC/GL 77-2011' in *Codex texts on antimicrobial resistance,* available at http://www.fao.org/3/a-i4296t.pdf.

Callaway, T, Edrington, T, Rychlik, J, Genovese, K, Poole, T, Jung, YS, Bischoff, K, Anderson, R & Nisbet, DJ 2003, 'Ionophores: their use as ruminant growth promotants and impact on food safety', *Curr Issues Intest Microbiol,* vol. 4, pp. 43-51.

Cantón, R & Morosini, M 2011, 'Emergence and spread of antibiotic resistance following exposure to antibiotics', *FEMS Microbiol Rev*, vol. 35, pp. 977-991.

Cantón, R & Ruiz-Garbajosa, P 2011, 'Co-resistance: an opportunity for the bacteria and resistance genes', *Curr Opin Pharmacol*, vol. 11, pp. 477-485.

Carattoli, A 2008, 'Animal reservoirs for extended-spectrum beta-lactamase producers', *Clin Microbiol Infect*, vol. 14, pp. S117-123.

---- 2013, 'Plasmids and the spread of resistance', *Int J Med Microbiol,* vol. 303, pp. 298-304.

Casewell, M, Friis, C, Marco, E, McMullin, P & Phillips, I 2003, 'The European ban on growth-promoting antibiotics and emerging consequences for human and animal health', *J Antimicrob Chemother,* vol. 52, pp. 159-161.

Catry, B, Cavaleri, M, Baptiste, K, Grave, K, Grein, K, Holm, A, Jukes, H, Liebana, E, Navas, A, Mackay, D, Magiorakos, A, Romo, M, Moulin, G, Madero, C, Pomba, M, Powell, M, Pyörälä, S, Rantala, M, Ružauskas, M, Sanders, P, Teale, C, Threlfall, E, Törneke, K, van Duijkeren, E & Edo, J 2015, 'Use of colistin-containing products within the European Union and European Economic Area (EU/EEA): development of resistance in animals and possible impact on human and animal health', *Int J Antimicrob Agents,* available at doi: 10.1016/j.ijantimicag.2015.06.005.

CDC 2002, 'Outbreak of multidrug-resistant Salmonella newport--United States, January-April 2002', *MMWR Morb Mortal Wkly Rep*, vol. 51, pp. 545-548.

---- 2017, *National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS)*, available at https://www.cdc.gov/narms/.

Cheng, A, Turnidge, J, Collignon, P, Looke, D, Barton, M & Gottlieb, T 2012, 'Control of fluoroquinolone resistance through successful regulation, Australia', *Emerg Infect Dis*, vol. 18, pp. 1453-1460.

Chuang, Y & Huang, Y 2014, 'Livestock-associated meticillin-resistant Staphylococcus aureus in Asia: an emerging issue?', *Int J Antimicrob Agents*, vol. 45, pp. 334-340.

CLSI 2013, *VET-01-A4 – Performance Standards for Antimicrobial Disc and Dilution Susceptibility Tests for Bacteria Isolated from Animals*, Approved Standard, 4th edition, available at http://shop.clsi.org/site/Sample_pdf/VET01A4_sample.pdf.

---- 2014a, *VET-03-A/VET-04S2: Performance Standards for Antimicrobial Susceptibility Testing of Bacteria Isolated From Aquatic Animals*, Second Informational Supplement, available at http://shop.clsi.org/c.1253739/site/Sample_pdf/VET03VET04S2_sample.pdf.

---- 2014b, *VET03/VET04-S2: Performance Standards for Antimicrobial Susceptibility Testing of Bacteria Isolated From Aquatic Animals*, Second Informational Supplement, available at http://shop.clsi.org/c.1253739/site/Sample_pdf/VET03VET04S2_sample.pdf.

---- 2017, *CLSI standards center*, available at http://clsi.org/standards/.

Cogliani, C, Goossens, H & Grek, C 2011, 'Restricting antimicrobial use in food animals: lessons from Europe', *Microbe,* vol. 6, pp. 274-279.

Commission on Antibacterial Feed Additives 1997, *Antibacterial Feed Additives*, Ministry of Agriculture, Stockholm.

Coulter, S, Merollini, K, Roberts, J, Graves, N & Halton, K 2015, 'The need for cost-effectiveness analyses of antimicrobial stewardship programmes: A structured review', *Int J Antimicrob Agents,* vol. 46, pp. 140-149.

Cuny, C, Friedrich, A, Kozytska, S, Layer, F, Nübel, U, Ohlsen, K, Strommenger, B, Walther, B, Wieler, L & Witte, W 2010, 'Emergence of methicillin-resistant Staphylococcus aureus (MRSA) in different animal species', *Int J Med Microbiol*, vol. 300, pp. 109-117.

D'Costa, V, King, C, Kalan, L, Morar, M, Sung, W, Schwarz, C, Froese, D, Zazula, G, Calmels, F, Debruyne, R, Golding, G, Poinar, H & Wright, G 2011, 'Antibiotic resistance is ancient', *Nature*, vol. 477, pp. 457-461.

da Costa, P, Loureiro, L & Matos, A 2013, 'Transfer of multidrug-resistant bacteria between intermingled ecological niches: the interface between humans, animals and the environment', *Int J Environ Res Public Health*, vol. 10, pp. 278-294.

DAFF 2007, 'Pilot surveillance program for antimicrobial resistance in bacteria of animal origin', available at http://www.agriculture.gov.au/SiteCollectionDocuments/ag-food/food/food-safety/antimicrobial/AMR-pilot-survey-report.pdf.

Davies, J & Davies, D 2010, 'Origins and evolution of antibiotic resistance', *Microbiol Mol Biol Rev*, vol. 74, pp. 417-433.

Davies, S 2015, *A ticking time bomb: the infectious threat of antibiotic resistance*, available at http://www.oxfordmartin.ox.ac.uk/event/2056.

de Been, M, Lanza, V, de Toro, M, Scharringa, J, Dohmen, W, Du, Y, Hu, J, Lei, Y, Li, N, Tooming-Klunderud, A, Heederik, D, Fluit, A, Bonten, M, Willems, R, de la Cruz, F & van Schaik, W 2014, 'Dissemination of cephalosporin resistance genes between Escherichia coli strains from farm animals and humans by specific plasmid lineages', *PLoS One*, vol. 10, pp. e1004776.

de Jong, A, Smet, A, Ludwig, C, Stephan, B, De Graef, E, Vanrobaeys, M & Haesebrouck, F 2014, 'Antimicrobial susceptibility of Salmonella isolates from healthy pigs and chickens (2008-2011)', *Vet Microbiol*, vol. 171, pp. 298-306.

Department of Health 2015, 'National Antimicrobial Resistance Strategy 2015-2019', available at http://www.health.gov.au/internet/main/publishing.nsf/Content/1803C433C71415CACA257C8400121B1F/$File/amr-strategy-2015-2019.pdf.

---- 2016, 'Implementation Plan: Australia's First National Antimicrobial Resistance Strategy 2015–2019', available at http://www.health.gov.au/internet/main/publishing.nsf/Content/1803C433C71415CACA257C8400121B1F/$File/AMR-Implementation-Plan.pdf.

Department of Health and Ageing 2000, 'The Commonwealth Government Response to the Report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR)', available at http://www.health.gov.au/internet/main/publishing.nsf/Content/health-pubs-jetacar-cnt.htm.

Deshpande, L, Pfaller, M & Jones, R 2000, 'In vitro activity of ceftiofur tested against clinical isolates of Escherichia coli and Klebsiella pneumoniae including extended spectrum beta-lactamase producing strains', *Int J Med Microbiol*, vol. 15, pp. 271-275.

Domingues, S, Nielsen, K & da Silva, G 2012, 'Various pathways leading to the acquisition of antibiotic resistance by natural transformation', *Mob Genet Elements*, vol. 2, pp. 257-260.

Done, HY, Venkatesan, AK & Halden, RU 2015, 'Does the recent growth of aquaculture create antibiotic resistance threats different from those associated with land animal production in agriculture?', *AAPS Journal*, vol. 17, pp. 513–524, available at http://pubmedcentralcanada.ca/pmcc/articles/PMC4406955/.

Dong, Y, Zhao, X, Domagala, J & Drlica, K 1999, 'Effect of fluoroquinolone concentration on selection of resistant mutants of Mycobacterium bovis BCG and Staphylococcus aureus', *Antimicrob Agents Chemother*, vol. 43, pp. 1756-1758.

Doron, S & Davidson, L 2011, 'Antimicrobial stewardship', *Mayo Clin Proc*, vol. 86, pp. 1113-1123.

Drlica, K & Zhao, X 2007, 'Mutant selection window hypothesis updated', *Clin Infect Dis*, vol. 44, pp. 681-688.

E. M. A. Committee for Medicinal Products for Veterinary Use, Efsa Panel on Biological Hazards, Murphy, D, Ricci, A, Auce, Z, Beechinor, JG, Bergendahl, H, Breathnach, R, Bureš, J, Duarte Da Silva, JP, Hederová, J, Hekman, P, Ibrahim, C, Kozhuharov, E, Kulcsár, G, Lander Persson, E, Lenhardsson, JM, Mačiulskis, P, Malemis, I, Markus-Cizelj, L, Michaelidou-Patsia, A, Nevalainen, M, Pasquali, P, Rouby, J-C, Schefferlie, J, Schlumbohm, W, Schmit, M, Spiteri, S, Srčič, S, Taban, L, Tiirats, T, Urbain, B, Vestergaard, E-M, Wachnik-Święcicka, A, Weeks, J, Zemann, B, Allende, A, Bolton, D, Chemaly, M, Fernandez Escamez, PS, Girones, R, Herman, L, Koutsoumanis, K, Lindqvist, R, Nørrung, B, Robertson, L, Ru, G, Sanaa, M, Simmons, M, Skandamis, P, Snary, E, Speybroeck, N, Ter Kuile, B, Wahlström, H, Baptiste, K, Catry, B, Cocconcelli, PS, Davies, R, Ducrot, C, Friis, C, Jungersen, G, More, S, Muñoz Madero, C, Sanders, P, Bos, M, Kunsagi, Z, Torren Edo, J, Brozzi, R, Candiani, D, Guerra, B, Liebana, E, Stella, P, Threlfall, J & Jukes, H 2017, 'EMA and EFSA Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety (RONAFA)', *EFSA Journal*, vol. 15, pp. e04666-n/a.

EFSA 2016, 'The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2014', *EFSA Journal*, 14, 4380-n/a, available at http://dx.doi.org/10.2903/j.efsa.2016.4380.

---- 2017a, 'Risk for the development of Antimicrobial Resistance (AMR) due to feeding of calves with milk containing residues of antibiotics', *EFSA Journal*, 15, e04665-n/a, available at http://dx.doi.org/10.2903/j.efsa.2017.4665.

---- 2017b, 'EMA and EFSA Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety (RONAFA)', *EFSA Journal*, 15, e04666-n/a, available at http://dx.doi.org/10.2903/j.efsa.2017.4666.

EMA 2015, *Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances*, EMA/CVMP/261180/2012,

Endtz, H, Ruijs, G, van Klingeren, B, Jansen, W, van der Reyden, T & Mouton, R 1991, 'Quinolone resistance in campylobacter isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine', *J Antimicrob Chemother*, vol. 27, pp. 199-208.

Esiobu, N, Armenta, L & Ike, J 2002, 'Antibiotic resistance in soil and water environments', *Int J Environ Health Res*, vol. 12, pp. 133-144.

EUCAST 2017, *The European Committee on Antimicrobial Susceptibility Testing - EUCAST*, available at http://www.eucast.org/.

European Commission 2005, 'Ban on antibiotics as growth promoters in animal feed enters into effect', available at http://europa.eu/rapid/press-release_IP-05-1687_en.htm.

Ewers, C, Stamm, I, Pfeifer, Y, Wieler, L, Kopp, P, Schønning, K, Prenger-Berninghoff, E, Scheufen, S, Stolle, I, Günther, S & Bethe, A 2014, 'Clonal spread of highly successful ST15-CTX-M-15 Klebsiella pneumoniae in companion animals and horses', *J Antimicrob Chemother*, vol. 69, pp. 2676-2680.

Fàbrega, A, Madurga, S, Giralt, E & Vila, J 2009, 'Mechanism of action of and resistance to quinolones', *Microb Biotechnol*, vol. 2, pp. 40-61.

Fairles, J 2013, 'The veterinarian's role in antimicrobial stewardship', *Can Vet J,* vol. 54, pp. 207-209.

Falgenhauer, L, Ghosh, H, Guerra, B, Yao, Y, Fritzenwanker, M, Fischer, J, Helmuth, R, Imirzalioglu, C & Chakraborty, T 2017, 'Comparative genome analysis of IncHI2 VIM-1 carbapenemase-encoding plasmids of

Escherichia coli and Salmonella enterica isolated from a livestock farm in Germany', *Vet Microbiol*, vol. 200, pp. 114-117.

FAO 1985, *Residues of veterinary drugs in food: report of a FAO/WHO joint consultation 29 October to 5 November 1984*, FAO Food Nutr Pap. 32, FAO Rome.

---- 2010, *The State of World Fisheries and Aquaculture, 2010*, FAO Fisheries and Aquaculture Department Rome, available at http://www.fao.org/docrep/013/i1820e/i1820e.pdf.

---- 2015, *Antimicrobial resistance*, available at http://www.fao.org/antimicrobial-resistance/en/.

Fard, R, Heuzenroeder, M & Barton, M 2011, 'Antimicrobial and heavy metal resistance in commensal enterococci isolated from pigs', *Vet Microbiol*, vol. 148, pp. 276-282.

FDA 2012, 'Guidance for Industry #209: the judicious use of medically important antimicrobial drugs in food-producing animals', *Food and Drug Administration Center for Veterinary Medicine*, available at http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf.

---- 2013, 'Guidance for Industry #213: 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 with GFI #209', *Food and Drug Administration Center for Veterinary Medicine*, available at http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf.

---- 2015, 'Veterinary Feed Directive', available at https://www.federalregister.gov/articles/2015/06/03/2015-13393/veterinary-feed-directive#h-7.

---- 2016, *FDA releases final rule related to the reporting of antimicrobial sales and distribution information*, available at https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm499990.htm.

Feinman, S 1998, 'Antibiotics in animal feed – drug resistance revisited', *Amer Soc Microbiol News,* vol. 64, pp. 24-30.

Finance and Public References Committee 2013, 'Progress in the implementation of the recommendations of the 1999 Joint Expert Technical Advisory Committee on Antibiotic Resistance', available at http://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Finance_and_Public_Administration/Completed_inquiries/2010-13/jetacar/report/index.

Fleming, A 1929, 'On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenzae', *Br J Exp Pathol*, vol. 10, pp. 226-236.

---- 1945, *Penicillin*, Nobel Lecture, available at http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.pdf.

Fluit, A 2012, 'Livestock-associated Staphylococcus aureus', *Clin Microbiol Infect*, vol. 18, pp. 735-744.

Fone, D & Barker, R 1994, 'Associations between human and farm animal infections with Salmonella typhimurium DT104 in Herefordshire', *Commun Dis Rep CDR Rev*, vol. 4, pp. R136-140.

Forslund, K, Sunagawa, S, Coelho, LP & Bork, P 2014, 'Metagenomic insights into the human gut resistome and the forces that shape it', 36, 316–329, available at http://onlinelibrary.wiley.com/doi/10.1002/bies.201300143/full.

Gibson, J, Cobbold, R, Kyaw-Tanner, M, Heisig, P & Trott, D 2010, 'Fluoroquinolone resistance mechanisms in multidrug-resistant Escherichia coli isolated from extraintestinal infections in dogs', *Vet Microbiol*, vol. 146, pp. 161-166.

Giske, C 2015, 'Contemporary resistance trends and mechanisms for the old antibiotics colistin, temocillin, fosfomycin, mecillinam and nitrofurantoin', *Clin Microbiol Infect*, available at http://www.sciencedirect.com/science/article/pii/S1198743X15005546.

Grave, K, Jensen, VF, Odensvik, K, Wierup, M & Bangen, M 2006, 'Usage of veterinary therapeutic antimicrobials in Denmark, Norway and Sweden following termination of antimicrobial growth promoter use', *Prev Vet Med*, vol, 75, pp. 123-132, available at http://www.sciencedirect.com/science/article/pii/S0167587706000559.

Graveland, H, Duim, B, van Duijkeren, E, Heederik, D & Wagenaar, J 2011, 'Livestock-associated methicillin-resistant Staphylococcus aureus in animals and humans', *Int J Med Microbiol*, vol. 301, pp. 630-634.

Griggs, D, Hall, M, Jin, Y & Piddock, L 1994, 'Quinolone resistance in veterinary isolates of Salmonella', *Antimicrob Agents Chemother*, vol. 33, pp. 1173-1189.

Groves, M, O'Sullivan, M, Brouwers, H, Chapman, T, Abraham, S, Trott, D, Al Jassim, R, Coombs, G, Skov, R & D, J 2014, 'Staphylococcus aureus ST398 detected in pigs in Australia', *J Antimicrob Chemother*, vol. 69, pp. 1426-1428.

Gudding R & Van Muiswinkel, W 2013, 'A history of fish vaccination: science-based disease prevention in aquaculture', *Fish Shellfish Immunol*, vol. 35, pp. 1683-1688.

Guerra, B, Fischer, J & Helmuth, R 2014, 'An emerging public health problem: acquired carbapenemase-producing microorganisms are present in food-producing animals, their environment, companion animals and wild birds', *Vet Microbiol*, vol. 171, pp. 290-297.

Hao, H, Cheng, G, Iqbal, Z, Ai, X, Hussain, H, Huang, L, Dai, M, Wang, Y, Liu, Z & Yuan, Z 2014, 'Benefits and risks of antimicrobial use in food-producing animals', *Front Microbiol*, vol. 5, pp. 288.

Harrison, E, Weinert, L, Holden, M, Welch, J, Wilson, K, Morgan, F, Harris, S, Loeffler, A, Boag, A, Peacock, S, Paterson, G, Waller, A, Parkhill, J & Holmes, M 2014, 'A shared population of epidemic methicillin-resistant Staphylococcus aureus 15 circulates in humans and companion animals', *MBio*, vol. 5, pp. e00985-13.

Hart, W, Heuzenroeder, M & Barton, M 2004, 'Antimicrobial resistance in Campylobacter spp., Escherichia coli and enterococci associated with pigs in Australia', *J Vet Med B Infect Dis Vet Public Health*, vol. 51, pp. 216-221.

Hawkey, P & Jones, A 2009, 'The changing epidemiology of resistance', *J Antimicrob Chemother*, vol. 64, pp. i3-10.

Herrero-Fresno, A, Zachariasen, C, Hansen, MH, Nielsen, A, Hendriksen, RS, Nielsen, SS & Olsen, JE 2016, 'Apramycin treatment affects selection and spread of a multidrug-resistant Escherichia coli strain able to colonize the human gut in the intestinal microbiota of pigs', *Veterinary Research*, vol. 47, pp. 12.

Heuer, H, Schmitt, H & Smalla, K 2011, 'Antibiotic resistance gene spread due to manure application on agricultural fields', *Curr Opin Microbiol*, vol. 14, pp. 236-243.

Ho, P, Leung, L, Chow, K, Lai, E, Lo, W & Ng, T 2014, 'Prevalence of aminoglycoside modifying enzyme and 16S ribosomal RNA methylase genes among aminoglycoside-resistant Escherichia coli isolates', *J Microbiol Immunol Infect*, vol. 49, pp. 123-126.

Hoa, P, Managaki, S, Nakada, N, Takada, H, Shimizu, A, Anh, D, Viet, P & Suzuki, S 2011, 'Antibiotic contamination and occurrence of antibiotic-resistant bacteria in aquatic environments of northern Vietnam', *Sci Total Environ*, vol. 409, pp. 2894-2901.

Holman, D & Chénier, M 2014, 'Temporal changes and the effect of subtherapeutic concentrations of antibiotics in the gut microbiota of swine', *FEMS Microbiol Ecol*, vol. 90, pp. 599-608.

Huddleston, J 2014, 'Horizontal gene transfer in the human gastrointestinal tract: potential spread of antibiotic resistance genes', *Infect Drug Resist*, vol. 7, pp. 167-176.

Hughes, P & Heritage, J 2002, 'Antibiotic growth-promoters in food animals', *AGRIPPA*, available at http://www.fao.org/docrep/ARTICLE/AGRIPPA/555_EN.HTM.

Huijsdens, X, van Dijke, B, Spalburg, E, van Santen-Verheuvel, M, Heck, M, Pluister, G, Voss, A, Wannet, W & de Neeling, A 2006, 'Community-acquired MRSA and pig-farming', *Ann Clin Microbiol Antimicrob*, vol. 5, pp. 26.

Huttner, A, Harbarth, S, Carlet, J, Cosgrove, S, Goossens, H, Holmes, A, Jarlier, V, Voss, A & Pittet, D 2013, 'Antimicrobial resistance: a global view from the 2013 World Healthcare-Associated Infections Forum', *Antimicrobial Resistance and Infection Control*, 2, available at https://aricjournal.biomedcentral.com/articles/10.1186/2047-2994-2-31.

Ingram, P, Rogers, B, Sidjabat, H, Gibson, J & Inglis, T 2013, 'Co-selection may explain high rates of ciprofloxacin non-susceptible Escherichia coli from retail poultry reared without prior fluoroquinolone exposure', *J Med Microbiol*, vol. 62, pp. 1743-1746.

Iyer, A, Barbour, E, Azhar, E, El Salabi, A, Hassan, H, Qadri, I, Chaudhary, A, Abuzenadah, A, Kumosani, T, Damanhouri, G, Alawi, M, Na'was, T, Abdel Nour, A & Harakeh, S 2013, 'Transposable elements in Escherichia coli antimicrobial resistance', *Adv Biosci Biotechnol*, vol. 4, pp. 415-423.

Izzo, M, Mohler, V & House, J 2011, 'Antimicrobial susceptibility of Salmonella isolates recovered from calves with diarrhoea in Australia', *Aust Vet J,* vol. 89, pp. 402-408.

Jacoby, G 2009, 'AmpC beta-lactamases', *Clin Microbiol Rev*, vol. 22, pp. 161-182.

Jacoby, G, Strahilevitz, J & Hooper, D 2014, 'Plasmid-mediated quinolone resistance', *Microbiol Spectr*, 2, available at doi: 10.1128/microbiolspec.PLAS-0006-2013.

Jensen, V, Jakobsen, L, Emborg, H, Seyfarth, A & Hammerum, A 2006, 'Correlation between apramycin and gentamicin use in pigs and an increasing reservoir of gentamicin-resistant Escherichia coli', *J Antimicrob Chemother*, vol. 58, pp. 101-107.

JETACAR 1999, *The Use of Antibiotics in Food Producing Animals: Antibiotic-resistant bacteria in animals and humans*, Department of Health and Aged Care/Department of Agriculture, Fisheries and Forestry, Canberra.

---- 2000, 'The Commonwealth Government response to the report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance', available at www.aph.gov.au/DocumentStore.ashx?id=1c7e52de-45fc-4657-a742-651a7ff8f234.

Johnson, A, Burns, L, Woodford, N, Threlfall, E, Naidoo, J, Cooke, E & George, R 1994, 'Gentamicin resistance in clinical isolates of Escherichia coli encoded by genes of veterinary origin', *J Med Microbiol*, vol. 40, pp. 221-226.

Jordan, D, Simon, J, Fury, S, Moss, S, Giffard, P, Maiwald, M, Southwell, P, Barton, M, Axon, J, Morris, S & Trott, D 2011, 'Carriage of methicillin-resistant Staphylococcus aureus by veterinarians in Australia', *Aust Vet J*, vol. 89, pp. 152-159.

Kadlec, K, Feßler, AT, Hauschild, T & Schwarz, S 2012, 'Novel and uncommon antimicrobial resistance genes in livestock-associated methicillin-resistant Staphylococcus aureus', *Clin Microbiol Infect*, vol. 18, pp. 745-755.

Kim, M-C, Cha, M-H, Ryu, J-G & Woo, G-J 2017, 'Characterization of vancomycin-resistant Enterococcus faecalis and Enterococcus faecium isolated from fresh produces and human fecal samples', *Foodborne Pathog Dis*, vol. 14, pp, 195-201, available at http://online.liebertpub.com/doi/10.1089/fpd.2016.2188.

Kümmerer, K 2009, 'Antibiotics in the aquatic environment--a review--part II', *Chemosphere,* vol. 75, pp. 435-441.

Lambert, T 2012, 'Antibiotics that affect the ribosome', *Rev Sci Tech*, vol. 31, pp. 57-64.

Laxminarayan, R, Matsoso, P, Pant, S, Brower, C, Røttingen, J-A, Klugman, K & Davies, S 2015, 'Access to effective antimicrobials: a worldwide challenge', *The Lancet*, vol. 387, pp, 168-175, available at http://dx.doi.org/10.1016/S0140-6736(15)00474-2.

Lazarus, B, Paterson, D, Mollinger, J & Rogers, B 2015, 'Do human extraintestinal Escherichia coli infections resistant to expanded-spectrum cephalosporins originate from food-producing animals? A systematic review', *Clin Infect Dis,* vol. 60, pp. 439-452.

Lean, I 2013, 'Effects of retailer pressure on the efficiency of agricultural industries', *Anim Prod Sci*, vol. 53, pp. 1143-1148.

Leonard, F & Markey, B 2008, 'Meticillin-resistant Staphylococcus aureus in animals: a review', *Vet J,* vol. 175, pp. 27-36.

Levy, S 1985, 'Man, animals and antibiotic resistance', *Pediatr Infect Dis,* vol. 4, pp. 3-5.

Levy, SB 1978, 'Emergence of antibiotic-resistant bacteria in the intestinal flora of farm inhabitants ', *J Infect Dis, vol.* 137, pp. 688-690, available at http://www.jstor.org/stable/30111379

Li, L, Wang, B, Feng, S, Li, J, Wu, C, Wang, Y, Ruan, X & Zeng, M 2014a, 'Prevalence and characteristics of extended-spectrum β-lactamase and plasmid-mediated fluoroquinolone resistance genes in Escherichia coli isolated from chickens in Anhui province, China', *PLoS One,* vol. 20, pp. e104356.

Li, X, Watanabe, N, Xiao, C, Harter, T, McCowan, B, Liu, Y & Atwill, E 2014b, 'Antibiotic-resistant E. coli in surface water and groundwater in dairy operations in Northern California', *Environ Monit Assess*, vol. 186, pp. 1253-1260.

Li, X, Plésiat, P & Nikaido, H 2015, 'The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria', *Clin Microbiol Rev*, vol. 28, pp. 337-418.

Linton, A 1984, 'Antibiotic-resistant bacteria in animal husbandry', *Br Med Bull*, vol. 40, pp. 91-95.

Liu, Y-Y, Wang, Y, Walsh, TR, Yi, L-X, Zhang, R, Spencer, J, Doi, Y, Tian, G, Dong, B, Huang, X, Yu, L-F, Gu, D, Ren, H, Chen, X, Lv, L, He, D, Zhou, H, Liang, Z, Liu, J-H & Shen, J 2015, 'Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study', *Lancet Infect Dis*, vol. 16, pp. 161-168, available at http://dx.doi.org/10.1016/S1473-3099(15)00424-7.

Lloyd, D 2007, 'Reservoirs of antimicrobial resistance in pet animals', *Clin Infect Dis*, vol. 45, pp. S148-152.

Loeffler, A & Lloyd, D 2010, 'Companion animals: a reservoir for methicillin-resistant Staphylococcus aureus in the community?', *Epidemiol Infect*, vol. 138, pp. 595-605.

Looft, T, Allen, H, Cantarel, B, Levine, U, Bayles, D, Alt, D, Henrissat, B & Stanton, T 2014, 'Bacteria, phages and pigs: the effects of in-feed antibiotics on the microbiome at different gut locations', *ISMEJ*, vol. 8, pp. 1566-1576.

Love, D, Davis, M, Bassett, A, Gunther, A & Nachman, K 2011, 'Dose imprecision and resistance: free-choice medicated feeds in industrial food animal production in the United States', *Environ Health Perspect*, vol. 119, pp. 279-283.

Lupindu, A, Dalsgaard, A, Msoffe, P, Ngowi, H, Mtambo, M & Olsen, J 2015, 'Transmission of antibiotic-resistant Escherichia coli between cattle, humans and the environment in peri-urban livestock keeping communities in Morogoro, Tanzania', *Prev Vet Med*, vol. 118, pp. 477-482.

Madec, JY, Haenni, M, Nordmann, P & Poirel, L 2017, 'Extended-spectrum β-lactamase/AmpC- and carbapenemase-producing Enterobacteriaceae in animals: a threat for humans?', *Clin Microbiol Infect*, available at http://dx.doi.org/10.1016/j.cmi.2017.01.013.

Magiorakos, AP, Srinivasan, A, Carey, RB, Carmeli, Y, Falagas, ME, Giske, CG, Harbarth, S, Hindler, JF, Kahlmeter, G, Olsson-Liljequist, B, Paterson, DL, Rice, LB, Stelling, J, Struelens, MJ, Vatopoulos, A, Weber, JT & Monnet, DL 2012, 'Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance', *Clin Microbiol Infect*, vol. 18, pp. 268-281.

Malik, S, Coombs, G, O'Brien, F, Peng, H & Barton, M 2006, 'Molecular typing of methicillin-resistant staphylococci isolated from cats and dogs', *J Antimicrob Chemother*, vol. 58, pp. 428-431.

Mathers, A, Peirano, G & Pitout, J 2015, 'The role of epidemic resistance plasmids and international high-risk clones in the spread of multidrug-resistant Enterobacteriaceae', *Clin Microbiol Rev*, vol. 28, pp. 565-591.

McManus, P, Stockwell, V, Sundin, G & Jones, A 2002, 'Antibiotic use in plant agriculture', *Annu Rev Phytopathol*, vol. 40, pp. 443-465.

McMillan, K, Moore, SC, McAuley, CM, Fegan, N & Fox, EM 2016, 'Characterization of Staphylococcus aureus isolates from raw milk sources in Victoria, Australia', *BMC Microbiol*, vol. 16, pp. 169.

Meireles, D, Leite-Martins, L, Bessa, L, Cunha, S, Fernandes, R, de Matos, A, Manaia, C & Martins da Costa, P 2015, 'Molecular characterization of quinolone resistance mechanisms and extended-spectrum β-lactamase production in Escherichia coli isolated from dogs', *Comp Immunol Microbiol Infect Dis*, vol. 41, pp. 43-48.

Melnyk, A, Wong, A & Kassen, R 2014, 'The fitness costs of antibiotic resistance mutations', *Evol Appl*, vol. 8, pp. 273-283.

Michael, G, Freitag, C, Wendlandt, S, Eidam, C, Feßler, A, Lopes, G, Kadlec, K & Schwarz, S 2015, 'Emerging issues in antimicrobial resistance of bacteria from food-producing animals', *Future Microbiol*, vol. 10, pp. 427-443.

Miflin, J, Templeton, J & Blackall, P 2007, 'Antibiotic resistance in Campylobacter jejuni and Campylobacter coli isolated from poultry in the South-East Queensland region', *J Antimicrob Chemother*, vol. 59, pp. 775-778.

Millet, S & Maertens, L 2011, 'The European ban on antibiotic growth promoters in animal feed: from challenges to opportunities', *Vet J*, vol. 187, pp. 143-144.

Miranda, C, Tello, A & Keen, P 2013, 'Mechanisms of antimicrobial resistance in finfish aquaculture environments', *Front Microbiol*, vol. 4, pp. 233.

Moellering, R 2012, 'MRSA: the first half century', *J Antimicrob Chemother*, vol. 67, pp. 4-11.

Moodley, A, Damborg, P & Nielsen, S 2014, 'Antimicrobial resistance in methicillin susceptible and methicillin resistant Staphylococcus pseudintermedius of canine origin: literature review from 1980 to 2013', *Vet Microbiol*, vol. 171, pp. 337-341.

Moore, J, Barton, M, Blair, I, Corcoran, D, Dooley, J, Fanning, S, Kempf, I, Lastovica, A, Lowery, C, Matsuda, M, McDowell, D, McMahon, A, Millar, B, Rao, J, Rooney, P, Seal, B, Snelling, W & Tolba, O 2006, 'The epidemiology of antibiotic resistance in Campylobacter', *Microbes Infect*, vol. 8, pp. 1955-1966.

Müller, S, Janssen, T & Wieler, L 2014, 'Multidrug resistant Acinetobacter baumannii in veterinary medicine--emergence of an underestimated pathogen?', *Berl Munch Tierarztl Wochenschr*, vol. 127, pp. 435-446.

Ndi, O & Barton, M 2011, 'Incidence of class 1 integron and other antibiotic resistance determinants in Aeromonas spp. from rainbow trout farms in Australia', *J Fish Dis*, vol. 34, pp. 589-599.

Nelson, J, Chiller, T, Powers, J & Angulo, F 2007, 'Fluoroquinolone-resistant Campylobacter species and the withdrawal of fluoroquinolones from use in poultry: a public health success story', *Clin Infect Dis*, vol. 44, pp. 977-980.

Nguyen, F, Starosta, A, Arenz, S, Sohmen, D, Dönhöfer, A & Wilson, D 2014, 'Tetracycline antibiotics and resistance mechanisms', *Biol Chem*, vol. 395, pp. 559-575.

Nicolas-Chanoine, M, Bertrand, X & Madec, J 2014, 'Escherichia coli ST131, an intriguing clonal group', *Clin Micobiol Rev*, vol. 27, pp. 543-574.

Nikaido, H 2009, 'Multidrug resistance in bacteria', *Annu Rev Biochem*, vol. 78, pp. 119-146.

Nobel, Y, Cox, L, Kirigin, F, Bokulich, N, Yamanishi, S, Teitler, I, Chung, J, Sohn, J, Barber, C, Goldfarb, D, Raju, K, Abubucker, S, Zhou, Y, Ruiz, V, Li, H, Mitreva, M, Alekseyenko, A, Weinstock, G, Sodergren, E & Blaser, M 2015, 'Metabolic and metagenomic outcomes from early-life pulsed antibiotic treatment', *Nat Commun,* vol. 6, pp. 7486.

Novais, C, Freitas, A, Silveira, E, Antunes, P, Silva, R, Coque, T & Peixe, L 2013, 'Spread of multidrug-resistant Enterococcus to animals and humans: an underestimated role for the pig farm environment', *J Antimicrob Chemother*, vol. 68, pp. 2746-2754.

NRA 1998, *Vet Requirements Series: Guidelines for Registering Agricultural and Veterinary Chemicals*, NRA, Canberra.

O'Neill, J 2016, 'Tackling drug-resistant infections globally: final report and recommendations', *The review on antimicrobial resistance*, available at https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf.

Obeng, A, Rickard, H, Ndi, O, Sexton, M & Barton, M 2012a, 'Antibiotic resistance, phylogenetic grouping and virulence potential of Escherichia coli isolated from the faeces of intensively farmed and free range poultry', *Vet Microbiol*, vol. 154, pp. 305-315.

Obeng, A, Rickard, H, Sexton, M, Pang, Y, Peng, H & Barton, M 2012b, 'Antimicrobial susceptibilities and resistance genes in Campylobacter strains isolated from poultry and pigs in Australia', *J Appl Microbiol*, vol. 113, pp. 294-307.

Obeng, A, Rickard, H, Ndi, O, Sexton, M & Barton, M 2013, 'Comparison of antimicrobial resistance patterns in enterococci from intensive and free range chickens in Australia', *Avian Pathol,* vol. 42, pp. 45-54.

Ochiai, K, Yamanaka, T, Kimura, K & Sawada, O 1959, 'Transfer of resistance from resistant dysentery bacteria to E. coli and vice versa in their mixed culture', *[Nippon iji shinpō] Japanese medical journal*, vol. 1861, pp. 34-37.

OIE 2015a, *Antimicrobial agents and antimicrobial resistance*, available at http://www.oie.int/our-scientific-expertise/veterinary-products/antimicrobials/.

---- 2015b, *OIE list of antimicrobial agents of veterinary importance*, available at http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/Eng_OIE_List_antimicrobials_May2015.pdf.

---- 2015c, *Antimicrobial resistance (AMR)*, available at http://www.oie.int/for-the-media/amr/.

Page, SW 2012, 'Does antibiotic use in farmed animals pose a risk to human health? — No', *Med J Aust*, vol. 196, pp. 303, available at https://www.mja.com.au/journal/2012/196/5/does-antibiotic-use-farmed-animals-pose-risk-human-health-no.

Pál, C, Papp, B & Lázár, V 2015, 'Collateral sensitivity of antibiotic-resistant microbes', *Trends Microbiol*, vol. 23, pp. 401-407.

Pallo-Zimmerman, L, Byron, J & Graves, T 2010, 'Fluoroquinolones: then and now', *Compend Contin Educ Vet*, vol. 32, pp. E1-9.

Palmieri, C, Varaldo, P & Facinelli, B 2011, 'Streptococcus suis, an emerging drug-resistant animal and human pathogen', *Front Microbiol*, vol. 2, pp. 235.

Park, A 2014, 'Obama plan to fight antibiotic resistance 'disappointing,' critics say', *Time*.

Park, Y, Hwang, S, Hong, M & Kwon, K 2012, 'Use of antimicrobial agents in aquaculture', *Rev Sci Tech*, vol. 31, pp. 189-197.

Phillips, I 2007, 'Withdrawal of growth-promoting antibiotics in Europe and its effects in relation to human health', *Int J Antimicrob Agents*, vol. 30, pp. 101-107.

Pitcher, J, McLellan, J, Ballard, S, Grabsch, E & Grayson, M 2014, *Superbugs in the supermarket? Assessing the rate of contamination with multi-resistant (MDR) Gram-negative bacteria (GNB) in fresh Australian chicken and pork*, available at http://www.icaaconline.com/php/icaac2014abstracts/data/papers/2014/C-746.htm.

Platell, J, Johnson, J, Cobbold, R & Trott, D 2011, 'Multidrug-resistant extraintestinal pathogenic Escherichia coli of sequence type ST131 in animals and foods', *Vet Microbiol*, vol. 153, pp. 99-108.

Pomba, C, Rantala, M, Greko, C, Baptiste, KE, Catry, B, van Duijkeren, E, Mateus, A, Moreno, MA, Pyörälä, S, Ružauskas, M, Sanders, P, Teale, C, Threlfall, EJ, Kunsagi, Z, Torren-Edo, J, Jukes, H & Törneke, K 2017, 'Public health risk of antimicrobial resistance transfer from companion animals', *J Antimicrob Chemother*, vol. 72, pp. 957-968.

President's Council of Advisors on Science and Technology 2014, *Report to the President on combating antibiotic resistance*, available at https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf.

Price, LB, Stegger, M, Hasmanc, H, Aziza, M, Larsen, J, Andersen, PS, Pearson, T, Waters, AE, Foster, JT, Schuppa, J, Gillecea, J, Driebe, E, Liua, CML, Springer, B, Zdovc, I, Battisti, A, Franco, A, Żmudzkih, J, Schwarzi, S, Butaye, P, Jouyl, E, Pombam, C, Porreron, MC, Ruimyo, R, Smith, TC, Robinson, DA, Weeser, JS, Arriolas, CS, Yut, F, Laurentu, F, Keima, P, Skovb, R & Aarestrupc, FM 'Staphylococcus aureus CC398: host adaptation and emergence of methicillin resistance in livestock ', *mBio*, 3, e00305-11, available at http://mbio.asm.org/content/3/1/e00305-11.short.

Ramirez, M & Tolmasky, M 2010, 'Aminoglycoside modifying enzymes', *Drug Resist Updat*, vol. 13, pp. 151-171.

Reilly, A & Käferstein, F 1999, 'Food safety and products from aquaculture', *J Appl Microbiol*, vol. 85, pp. 249S-257S.

Reinthaler, F, Galler, H, Feierl, G, Haas, D, Leitner, E, Mascher, F, Melkes, A, Posch, J, Pertschy, B, Winter, I, Himmel, W, Marth, E & Zarfel, G 2013, 'Resistance patterns of Escherichia coli isolated from sewage sludge in comparison with those isolated from human patients in 2000 and 2009', *J Water Health*, vol. 11, pp. 13-20.

Rhouma, M, Beaudry, F & Letellier, A 2016, 'Resistance to colistin: what is the fate for this antibiotic in pig production?', *Int J Antimicrob Agents*, vol. 48, pp. 119-126.

Roberts, M 2011, 'Environmental macrolide-lincosamide-streptogramin and tetracycline resistant bacteria', *Front Microbiol*, vol. 2, pp. 40.

Roberts, MC, No, DB, Marzluff, JM, Delap, JH & Turner, R 2016, 'Vancomycin resistant Enterococcus spp. from crows and their environment in metropolitan Washington State, USA: Is there a correlation between VRE positive crows and the environment?', *Vet Microbiol*, vol. 194, pp. 48-54.

Rodríguez-Rojas, A, Rodríguez-Beltrán, J, Couce, A & Blázquez, J 2013, 'Antibiotics and antibiotic resistance: a bitter fight against evolution', *Int J Med Microbiol*, vol. 303, pp. 293-297.

Roy Chowdhury, P, McKinnon, J, Wyrsch, E, Hammond, J, Charles, I & Djordjevic, S 2014, 'Genomic interplay in bacterial communities: implications for growth promoting practices in animal husbandry', *Front Microbiol*, vol. 5, pp. 394.

Rubin, J & Pitout, J 2014, 'Extended-spectrum β-lactamase, carbapenemase and AmpC producing Enterobacteriaceae in companion animals', *Vet Microbiol*, vol. 170, pp. 10-18.

Sandegren, L 2014, 'Selection of antibiotic resistance at very low antibiotic concentrations', *Ups J Med Sci*, vol. 119, pp. 103-107.

SCAHLS 2014, *Antimicrobial Susceptibility Testing,* available at http://www.scahls.org.au/Procedures/Documents/ANZSDP/ANZSDP%20Antimicrobial%20Susceptibility%20Testing_AHC%20Approved.pdf

Schmiedel, J, Falgenhauer, L, Domann, E, Bauerfeind, R, Prenger-Berninghoff, E, Imirzalioglu, C & Chakraborty, T 2014, 'Multiresistant extended-spectrum β-lactamase-producing Enterobacteriaceae from humans, companion animals and horses in central Hesse, Germany', *BMC Microbiol*, vol. 14, pp. 187.

Schulfer, A & Blaser, M 2015, 'Risks of antibiotic exposures early in life on the developing microbiome', *PLoS Pathogens,* vol. 11, pp. e1004903.

Schultz, E, Haenni, M, Mereghetti, L, Siebor, E, Neuwirth, C, Madec, J, Cloeckaert, A & Doublet, B 2015, 'Survey of multidrug resistance integrative mobilizable elements SGI1 and PGI1 in Proteus mirabilis in humans and dogs in France, 2010-13', *J Antimicrob Chemother*, vol. 70, pp. 2543-2546.

Schwarz, S, Loeffler, A & Kadlec, K 2017, 'Bacterial resistance to antimicrobial agents and its impact on veterinary and human medicine', *Vet Dermatol*, vol. 28, pp. 82-e19.

Seiffert, S, Hilty, M, Perreten, V & Endimiani, A 2013, 'Extended-spectrum cephalosporin-resistant Gram-negative organisms in livestock: an emerging problem for human health?', *Drug Resist Updat*, vol. 16, pp. 22-45.

Shaheen, B, Nayak, R, Foley, S, Kweon, O, Deck, J, Park, M, Rafii, F & Boothe, D 2011, 'Molecular characterization of resistance to extended-spectrum cephalosporins in clinical Escherichia coli isolates from companion animals in the United States', *Antimicrob Agents Chemother*, vol. 55, pp. 5666-5675.

Shen, J, Wang, Y & Schwarz, S 2013, 'Presence and dissemination of the multiresistance gene cfr in Gram-positive and Gram-negative bacteria', *J Antimicrob Chemother*, vol. 68, pp. 1697-1706.

Shore, A & Coleman, D 2013, 'Staphylococcal cassette chromosome mec: recent advances and new insights', *Int J Med Microbiol*, vol. 303, pp. 350-359.

Shousha, A, Awaiwanont, N, Sofka, D, Smulders, F, Paulsen, P, Szostak, M, Humphrey, T & Hilbert, F 2015, 'Bacteriophages isolated from chicken meat and the horizontal transfer of antimicrobial resistance genes ', *Appl Environ Microbiol*, vol. 81, pp. 4600-4606.

Shryock, T & Page, S 2013, 'Performance uses of antimicrobial agents and non-antimicrobial alternatives' in *Antimicrobial Therapy in Veterinary Medicine*, 5th edition (Giguère, S, Prescott, J & Dowling, P), Wiley-Blackwell Ames.

Sidjabat, H, Hanson, N, Smith-Moland, E, Bell, J, Gibson, J, Filippich, L & Trott, D 2007, 'Identification of plasmid-mediated extended-spectrum and AmpC beta-lactamases in Enterobacter spp. isolated from dogs', *J Med Microbiol*, vol. 56, pp. 426-434.

Silley, P 2012, 'Susceptibility testing methods, resistance and breakpoints: what do these terms really mean? ', *Rev Sci Tech*, vol. 31, pp. 33-41.

Simjee, S, Silley, P, Werling, O & Bywater, R 2008, 'Potential confusion regarding the term “resistance” in epidemiological surveys', *J Antimicrob Chemother*, vol. 61, pp. 228-229.

Slifierz, MJ, Friendship, RM & Weese, JS 2015, 'Methicillin-resistant staphylococcus aureus in commercial swine herds is associated with disinfectant and zinc usage', *Appl Environ Microbiol*, vol. 81, pp. 2690-2695.

Smet, A, Martel, A, Persoons, D, Dewulf, J, Heyndrickx, M, Catry, B, Herman, L, Haesebrouck, F & Butaye, P 2008, 'Diversity of extended-spectrum beta-lactamases and class C beta-lactamases among cloacal Escherichia coli Isolates in Belgian broiler farms', *Antimicrob Agents Chemother*, vol. 52, pp. 1238-1243.

Smith, H 1967, 'The effect of the use of antibacterial drugs, particularly as feed additives, on the emergence of drug-resistant strains of bacteria in animals', *NZ Vet J,* vol. 15, pp. 153-166.

Smith, M, Jordan, D, Chapman, T, Chin, J, Barton, M, Do, T, Fahy, V, Fairbrother, J & Trott, D 2010, 'Antimicrobial resistance and virulence gene profiles in multi-drug resistant enterotoxigenic Escherichia coli isolated from pigs with post-weaning diarrhoea', *Vet Microbiol*, vol. 145, pp. 299-307.

Sparham, S 2015, *From paddock to (Agar) plate*, Australasian Society for Infectious Diseases Symposium Melbourne.

Stockwell, V & Duffy, B 2012, 'Use of antibiotics in plant agriculture', *Rev Sci Tech*, vol. 31, pp. 199-210.

Stohr, K 2000, 'Problems from antimicrobial use in farming', *Essential Drugs Monitor*, vol. 28-29, pp. 10-11.

Sun, J, Yang, M, Sreevatsan, S & Davies, PR 2015, 'Prevalence and characterization of Staphylococcus aureus in growing pigs in the USA', *PLOS ONE*, vol. 10, pp. e0143670.

Sundqvist, M 2014, 'Reversibility of antibiotic resistance', *Ups J Med Sci*, vol. 119, pp. 142-148.

Sundsfjord, A, Simonsen, G, Haldorsen, B, Haaheim, H, Hjelmevoll, S, Littauer, P & Dahl, K 2004, 'Genetic methods for detection of antimicrobial resistance', *APMIS,* vol. 112, pp. 815-837.

Swann, M 1969, *Use of Antibiotics in Animal Husbandry and Veterinary Medicine*, HM Stationary Office, London.

Tamang, MD, Moon, DC, Kim, S-R, Kang, HY, Lee, K, Nam, H-M, Jang, G-C, Lee, H-S, Jung, S-C & Lim, S-K 2017, 'Detection of novel oxazolidinone and phenicol resistance gene optrA in enterococcal isolates from food animals and animal carcasses', *Vet Microbiol*, vol. 201, pp. 252-256.

Tang, Y, Sahin, O, Pavlovic, N, LeJeune, J, Carlson, J, Wu, Z, Dai, L & Zhang, Q 2017, 'Rising fluoroquinolone resistance in Campylobacter isolated from feedlot cattle in the United States', *Scientific Reports*, vol. 7, pp. 494.

Teale, C & Mouin, G 2012, 'Prudent use guidelines: a review of existing guidelines', *Rev Sci Tech*, vol. 31, pp. 342-354.

The Lancet Infectious Diseases Commission 2013, 'Antibiotic resistance—the need for global solutions', *Lancet Infect Dis*, available at http://dx.doi.org/10.1016/S1473-3099(13)70318-9.

Theuretzbacher, U, Van Bambeke, F, Cantón, R, Giske, C, Mouton, J, Nation, R, Paul, M, Turnidge, J & Kahlmeter, G 2015, 'Reviving old antibiotics', *J Antimicrob Chemother*, vol. 70, pp. 2177-2181.

Trott, D 2013, 'β-lactam resistance in Gram-negative pathogens isolated from animals', *Curr Pharm Des*, vol. 19, pp. 239-249.

Tyrrell, JM, Wootton, M, Toleman, MA, Howe, RA, Woodward, M & Walsh, TR 2016, 'Genetic & virulence profiling of ESBL-positive E. coli from nosocomial & veterinary sources', *Vet Microbiol*, vol. 186, pp. 37-43.

Valentin, L, Sharp, H, Hille, K, Seibt, U, Fischer, J, Pfeifer, Y, Michael, G, Nickel, S, Schmiedel, J, Falgenhauer, L, Friese, A, Bauerfeind, R, Roesler, U, Imirzalioglu, C, Chakraborty, T, Helmuth, R, Valenza, G, Werner, G, Schwarz, S, Guerra, B, Appel, B, Kreienbrock, L & Käsbohrer, A 2014, 'Subgrouping of ESBL-producing Escherichia coli from animal and human sources: an approach to quantify the distribution of ESBL types between different reservoirs', *Int J Med Microbiol*, vol. 304, pp. 805-816.

Van Boeckel, T, Brower, C, Gilbert, M, Grenfell, B, Levin, S, Robinson, T, Teillant, A & Laxminarayan, R 2015, 'Global trends in antimicrobial use in food animals', *Proc Natl Acad Sci USA*, vol. 112, pp. 5649-5654.

van Hoek, A, Mevius, D, Guerra, B, Mullany, P, Roberts, A & Aarts, H 2011, 'Acquired antibiotic resistance genes: an overview', *Front Microbiol*, vol. 2, pp. 203.

Voss, A, Loeffen, F, Bakker, J, Klaassen, C & Wulf, M 2005, 'Methicillin-resistant Staphylococcus aureus in pig farming', *Emerg Infect Dis*, vol. 11, pp. 1965-1966.

Wall, BA, Mateus, A, Marshall, L, Pfeiffer, DU, Lubroth, J, Ormel, HJ, Otto, P & Patriarchi, A 2016, *Drivers, dynamics and epidemiology of antimicrobial resistance in animal production*, FAO Rome, available at http://www.fao.org/documents/card/en/c/d5f6d40d-ef08-4fcc-866b-5e5a92a12dbf/.

Walther, B, Monecke, S, Ruscher, C, Friedrich, A, Ehricht, R, Slickers, P, Soba, A, Wleklinski, C, Wieler, L & Lübke-Becker, A 2009, 'Comparative molecular analysis substantiates zoonotic potential of equine methicillin-resistant Staphylococcus aureus', *J Clin Microbiol*, vol. 47, pp. 704-710.

Walther, B, Lübke-Becker, A, Stamm, I, Gehlen, H, Barton, A, Janssen, T, Wieler, L & Guenther, S 2014, 'Suspected nosocomial infections with multi-drug resistant E. coli, including extended-spectrum beta-lactamase (ESBL)-producing strains, in an equine clinic', *Berl Munch Tierarztl Wochenschr*, vol. 127, pp. 421-427.

Wang, H, McEntire, J, Zhang, l, Li, X & Doyle, M 2012, 'The transfer of antibiotic resistance from food to humans: facts, implications and future directions', *Rev Sci Tech*, vol. 31, pp. 249-260.

Wasyl, D, Kern-Zdanowicz, I, Domańska-Blicharz, K, Zając, M & Hoszowski, A 2015, 'High-level fluoroquinolone resistant Salmonella enterica serovar Kentucky ST198 epidemic clone with IncA/C conjugative plasmid carrying bla(CTX-M-25) gene', *Vet MIcrobiol*, vol. 75, pp. 85-91.

Wegener, H 2003, 'Antibiotics in animal feed and their role in resistance development', *Curr Opin Microbiol*, vol. 6, pp. 439-445.

Wegener, H 2012, 'Antibiotic resistance—linking human and animal health' in *Improving Food Safety Through a One Health Approach: Workshop Summary*, (Institute of Medicine), National Academies Press Washington D.C.

Werner, G, Klare, I & Witte, W 1998, 'Association between quinupristin/dalfopristin resistance in glycopeptide-resistant Enterococcus faecium and the use of additives in animal feed', *Eur J Clin Microbiol Infect Dis*, vol. 17, pp. 401-402.

Werner, G, Coque, T, Franz, C, Grohmann, E, Hegstad, K, Jensen, L, van Schaik, W & Weaver, K 2013, 'Antibiotic resistant enterococci-tales of a drug resistance gene trafficker', *Int J Med Microbiol*, vol. 303, pp. 360-379.

WHO 2000, *WHO global principles for the containment of antimicrobial resistance in animals intended for food*, available at http://whqlibdoc.who.int/hq/2000/who_cds_csr_aph_2000.4.pdf.

---- 2001, *Global Strategy for Containment of Antimicrobial Resistance*, available at http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf?ua=1.

---- 2002, *Use of antimicrobials outside human medicine and resultant antimicrobial resistance in humans*, available at http://whqlibdoc.who.int/fact_sheet/2002/FS_268.pdf.

---- 2015a, *Draft global action plan on antimicrobial resistance*, available at http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_20-en.pdf?ua=1.

---- 2015b, *Drug resistance*, available at http://www.who.int/drugresistance/use/en/.

Wierup, M 2001, 'The Swedish experience of the 1986 year ban of antimicrobial growth promoters, with special reference to animal health, disease prevention, productivity, and usage of antimicrobials', *Microb Drug Resist*, vol. 7, pp. 183-190.

Williamson, D, Coombs, G & Nimmo, G 2014, 'Staphylococcus aureus 'Down Under': contemporary epidemiology of S. aureus in Australia, New Zealand, and the South West Pacific', *Clin Microbiol Infect*, vol. 20, pp. 597-604.

Wooldridge, M 2012, 'Evidence for the circulation of antimicrobial-resistant strains and genes in nature and especially between humans and animals', *Rev Sci Tech*, vol. 31, pp. 231-247.

World Economic Forum 2013, *The Dangers of Hubris on Human Health*, available at http://reports.weforum.org/global-risks-2013/risk-case-1/the-dangers-of-hubris-on-human-health/.

Xavier, BB, Lammens, C, Butaye, P, Goossens, H & Malhotra-Kumar, S 2016, 'Complete sequence of an IncFII plasmid harbouring the colistin resistance gene mcr-1 isolated from Belgian pig farms', *Journal of Antimicrobial Chemotherapy*, 71, 2342-2344, available at http://dx.doi.org/10.1093/jac/dkw191.

Yanat, B, Rodríguez-Martínez, J-M & Touati, A 2017, 'Plasmid-mediated quinolone resistance in Enterobacteriaceae: a systematic review with a focus on Mediterranean countries', *Eur J Clin Microbiol Infect Dis*, vol. 36, pp. 421-435.

Yang, Q, Ren, S, Niu, T, Guo, Y, Qi, S, Han, X, Liu, D & Pan, F 2014a, 'Distribution of antibiotic-resistant bacteria in chicken manure and manure-fertilized vegetables', *Environ Sci Pollut Res Int*, vol. 21, pp. 1231-1241.

Yang, T, Zeng, Z, Rao, L, Chen, X, He, D, Lv, L, Wang, J, Zeng, L, Feng, M & Liu, J 2014b, 'The association between occurrence of plasmid-mediated quinolone resistance and ciprofloxacin resistance in Escherichia coli isolates of different origins', *Vet Microbiol*, vol. 170, pp. 89-96.

Yazdankhah, S, Rudi, K & Bernhoft, A 2014, 'Zinc and copper in animal feed - development of resistance and co-resistance to antimicrobial agents in bacteria of animal origin', *Microb Ecol Health Dis*, available at http://dx.doi.org/10.3402/mehd.v25.25862.

Young, H 1993, 'Antimicrobial resistance spread in aquatic environments', *J Antimicrob Chemother*, vol. 31, pp. 627-635.

Yu, Z, Gunn, L, Wall, P & Fanning, S 2017, 'Antimicrobial resistance and its association with tolerance to heavy metals in agriculture production', *Food Microbiol*, vol. 64, pp. 23-32.

Zhang, A, Xu, C, Wang, H, Lei, C, Liu, B, Guan, Z, Yang, C, Yang, Y & Peng, L 2015, 'Presence and new genetic environment of pleuromutilin-lincosamide-streptogramin A resistance gene lsa(E) in Erysipelothrix rhusiopathiae of swine origin', *Vet Microbiol*, vol. 177, pp. 162-167.

Zhang, Y, Zhang, C, Parker, D, Snow, D, Zhou, Z & Li, X 2013, 'Occurrence of antimicrobials and antimicrobial resistance genes in beef cattle storage ponds and swine treatment lagoons', *Sci Total Environ*, vol. 463-464, pp. 631-638.