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Use of Antimicrobial Pharmaceuticals In Food-Producing Animals:

A Review

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Introduction

This document is a review of selected publications, legislation and guidelines related to the use of antimicrobial pharmaceuticals in food-producing animal production systems over approximately a ten year period, as of July 2014, with particular emphasis on the Canadian context.

Background

The development of antimicrobial agents has revolutionized animal and human health care (Morley et al., 2005). In addition to treating infectious diseases, antimicrobials are used at sub-therapeutic doses in livestock to promote growth, increase feed efficiency and prevent disease (Prescott, 2008).

The use of sub-therapeutic antimicrobials also allows animals to be housed at high densities by reducing the spread of disease (Green et al., 2010). There are many factors influencing a farm's environmental footprint, including land use, manufacture of feeds, transport of feeds, animals and animal products, waste management and energy consumption (Pruden et al., 2013) and sub-therapeutic use of antimicrobials reduce carbon footprints by increasing feed efficiency, which allows animals to achieve market weight more quickly, utilizing fewer resources (Stone et al., 2011).

Antimicrobial Resistance (AMR)

All uses of antimicrobial agents contribute to the emergence of antimicrobial-resistant micro-organisms and further promote the dissemination of resistant bacteria and resistance genes (FAO/WHO/OIE, 2008). Administration of antimicrobials impacts both foreign and commensal bacteria by selecting for traits that confer drug resistance (Raymond et al., 2006). Commensal species can act as a reservoir of resistance genes, which can be transmitted within or between bacterial strains via plasmids (Morley et al., 2005). An organism that is benign in one species might cause serious disease in others, including humans (Bos et al., 2012; Morley et al., 2005).

If the development of AMR continues unchecked, the end result could be that antimicrobial compounds will lose their effectiveness, and currently treatable ailments might again become intractable (Health Canada, 2002; Prescott, 2008; WHO, 2012). The continued emergence of resistant bacteria along with a lack of new antimicrobials on the market poses a worldwide human health threat (WHO, 2012). Antimicrobial pharmaceutical products are an essential component of modern veterinary care (Prescott, 2008). As such, veterinarians share the responsibility with human health practitioners, in addressing the problem of the potential impact on human and animal health as antibiotics become resistant and hence less effective (CVMA, 2009; CVMA, 2014; FAO/WHO/OIE, 2008; Guardabassi, 2008; Health Canada, 2002; OIE, 2013; WHO, 2000). A coordinated, multi-national strategy involving all sectors of healthcare and agriculture is needed to address this situation (CVMA, 2014; OIE, 2013; Prescott, 2008; WHO, 2012).

The link between antimicrobial use and the development of resistance is not a simple causal association (Gibbons et al., 2014; Tadesse et al., 2011), and can be direct (i.e. results from resistance among zoonotic infections) or indirect (i.e resistant genes pass from one bacteria to another) (Health Canada, 2002). However, every use of an antimicrobial increases the possibility for the development of resistance (British Veterinary Association, 2009). Studies on commensal bacteria in poultry and cattle have revealed rapid increases in antimicrobial susceptibility once selective pressures were removed (Kaneene et al., 2008; Sapkota et al, 2011). However, it is unclear whether this effect persists in the population beyond a couple of months (Kaneene et al., 2008; Kaneene et al., 2009). There are a multitude of factors that could potentially select for resistance (Singer & Hofacre, 2006). Furthermore, there appears to be no strong fitness cost to carrying resistance genes, meaning that these genes can persist in a bacterial population for decades (Álvarez-Fernández et al., 2012).

Resistant bacteria carried by food-producing animals can spread to people, through the consumption of inadequately cooked food, handling of raw food or by cross-contamination with other foods, through the environment (e.g. contaminated water) and through direct animal contact (WHO, 2012; Graveland et al., 2010). Antimicrobial residues and resistance genes can enter the environment through the application of manure to fields (Joy et al., 2013), wastewater lagoons (Peak et al., 2007) and soil (Braga et al., 2013). This environmental dissemination can impact the surrounding ecosystem, sympatric wildlife and neighbouring human communities (Joy et al., 2013; Navarro-Gonzales et al., 2013). Antimicrobials in feed are often water-soluble, with up to 90% of the dose administered excreted in urine, and up to 75% excreted in feces (Stone et al., 2011). In the United States (US), it has been demonstrated that medication protocols on beef feedlots impact wastewater levels of tetracycline resistance genes (Peak, 2007). A southern Ontario study examined presence of antimicrobial resistant *E. coli* in small mammals trapped near swine farms, landfills, residential areas or natural habitats. Although resistant *E. coli* was found in animals from all four sources, the animals trapped near the farms were significantly more likely to carry resistant strains (Allen et al., 2011).

In recent years, research on AMR has greatly increased (Webster, 2009). However, there is a need for accurate, species-specific data on drug usage in order to predict patterns of resistance (Thomson et al., 2008), as well as a need for a broad surveillance program (Health Canada, 2002; WHO, 2014) such as that provided in Canada by the Canadian Integrated Program for Antimicrobial Resistance Surveillance (Public Health Agency of Canada, 2008). Some studies have attempted to characterize medication practices in farm settings (Eagar et al, 2012; Menéndez Gonzáles et al., 2010), and some researchers have surveyed the prescribing practices of veterinarians, including the rationale behind selecting particular medication protocols for specific diagnoses (Thomson, 2010).

However, veterinarians may not have input on every treatment that occurs on the farms that they serve. Surveys of producers are an effective strategy for characterizing drug usage on commercial farms (Pardon et al., 2012), but may be compromised by recall bias and inadequate record-keeping practices (Zwald et al., 2004; Sawant et al., 2005). Collecting medication labels or containers provides figures on quantities dispensed and consumed, but this method of “garbage can audits” requires that all workers are compliant in properly disposing of the medication containers. Further, the producer may not be following the labelled indications for a given drug (Saini et al., 2012). Some studies have attempted to use multiple methods of gathering information, which allows cross-comparison (Carson, 2010). Implementing written treatment protocols and improvements in record keeping could be beneficial for producers to ensure consistent treatment. Such protocols and records could assist researchers by supplying data (Morley et al., 2005; Sawant et al., 2005).

Ranking of Antimicrobials According to Importance in Human Health

There is substantial overlap in the antimicrobial pharmaceuticals used in human and veterinary medicine (FAO/WHO/OIE, 2008; Prescott, 2008). Drug development has not kept pace with the emergence of new infectious pathogens (Agunos et al, 2013; WHO, 2000). To assist practitioners in their judicious selection of antimicrobials according to the risk to human health due to the development of resistance, the Veterinary Drugs Directorate, under the umbrella of Health Canada, has classified drugs into four categories from I to IV (Health Canada, 2009). Drugs that are used in treating severe infections in humans, which have few or no alternatives, are ranked as Category I (very high importance). Category I drugs are meant to be used sparingly in order to preserve their efficacy, and are considered “last resort” treatments for severe infections in humans (Health Canada, 2009). This category includes some important veterinary drugs such as ceftiofur, a third generation cephalosporin. While ceftiofur is not used in humans, it is closely related to some critical human drugs (Carson, 2010). Ceftiofur is approved for use in several food-producing animal species, including dairy cattle (Saini et al., 2012). Due to the fact that ceftiofur has no milk withdrawal time, it is widely used to treat mastitis, lameness and respiratory disease in dairy cattle (Pol & Ruegg, 2007; Saini et al., 2012).

There are some veterinary drugs that fall under Category IV, which have no current applications in human medicine. One example is the ionophores, which are widely used as coccidiostats in poultry (Chapman & Johnson, 2002), as well as in dairy cattle for prevention of ketosis and for improved feed efficiency (Duffield and Bagg, 2000). Although Category III or IV drugs are less important from a risk standpoint, loss of the low-category medications due to resistance would necessitate more intensive use of Category I and II drugs (Morley et al., 2005).

The list of drugs that are considered critically important for animal health and the list of drugs considered critically important for human health overlap for the classes including 3rd and 4th generation cephalosporins, quinolones (including fluoroquinolones), macrolides, penicillins and aminoglycosides (FAO/WHO/OIE, 2008). The three classes of antimicrobial drugs that should be addressed as the highest priority for the development of risk management strategies with respect to AMR are quinolones, 3rd and 4th generation cephalosporins, and macrolides (FAO/WHO/OIE, 2008).

Ranking drugs by importance may aid in choosing front-line therapies, but it does not provide guidance on targeting treatments for specific pathogens. A more practical solution might be to classify drugs into “lines” based on sensitivity testing (Prescott, 2008), although this approach would not capture regional or temporal variation in bacterial strains (Raymond et al., 2006).

Selecting drugs based on culture and sensitivity testing is commonly recommended for bacterial infections, including therapy of mastitis in milk-producing animals (Hill et al., 2009). However, culture and sensitivity testing adds to the cost involved, and delays the onset of treatment, which can negatively impact the outcome (Mavrogianni et al., 2011). Further, culture and sensitivity results do not guarantee successful treatment, as bacteria cultured *in vitro* may exhibit different responses *in vivo* (Barlow, 2011). For this reason, many producers and veterinarians prefer to start treatment with a broad-spectrum antibiotic in the absence of culture and sensitivity results (Hill et al., 2009). However, culture and sensitivity testing may be worthwhile in managing herd diseases such as mastitis, as it can help to establish a bacteriologic and sensitivity profile for the herd that will guide future treatment strategies (Mavrogianni et al., 2011).

Legislative And Policy/Guideline Considerations

Under Canadian law, a “drug” is broadly defined as any substance used to restore, correct or modify an organic state in a human being or animal. The definition encompasses treatment, mitigation and prevention of any disease state and its associated symptoms, as well as certain chemicals used to disinfect surfaces (Food and Drugs Act, 1985).

Veterinary drugs are subject to extensive testing to demonstrate safety and efficacy and to establish meat and milk withdrawal times. The results set a framework for drug labelling, including indications, species, dosage, frequency and duration of treatments, and route of administration (Fajt, 2011; Food and Drugs Act, 1985).

Any use that deviates from these parameters is considered extra-label drug use (CVMA, 2008; CVMA, 2009; CVMA, 2010) and is common practice in both human and veterinary medicine (CVMA, 2010; Health Canada, no date; Prescott, 2008). Extra-label drug use includes: use in a manner that is not in accordance with the approved label, package insert, or registration; use that is administered in a manner not explicitly stated on the approved label in regard to indication, dosage regimen, route or frequency of administration, duration of treatment, or target species; a drug approved for human but not veterinary use; active pharmaceutical ingredients; and compounded drugs (CVMA, 2010). Health Canada (no date) recommends that category I drugs not be used in an extra-label manner.

Extra-label drug use is particularly important in economically “minor” species, such as small ruminants and certain fowl species (Jacob et al., 2008; Pengov & Kirbis, 2009), since sponsor drug companies do not invest in the research necessary for product approval for minor species (Fajt, 2011). Furthermore, the drugs that are approved tend to have narrow indications (Moon et al., 2011), so that treatment options are limited. Extra-label use can be problematic, as dosages are not exact (Moon et al., 2011), which is a risk factor for the development of resistance (Prescott, 2008).

In Canada, veterinarians, pharmacists and approved lay outlets can sell antimicrobials. Some antimicrobials require a prescription and some are available over-the-counter. Canada is one of a few industrialized countries that allow the purchase of antimicrobials for use in food-producing animals without a prescription. Certain medications, such as dry cow treatments and some injectable antibiotics, can be purchased over-the-counter with no prescription (Livestock Medicines Act, 1990; Saini et al., 2012). There is no oversight by a veterinarian for the purchase and use of these drugs and elimination of over-the-counter sales of antimicrobials would help ensure that a veterinarian is involved in treatment decisions (Health Canada, 2002; Morley et al., 2011).

Most provinces license lay premises, including feed mills or dealers and retail outlets to sell veterinary antimicrobials (Health Canada, 2002). Non-prescription antimicrobials for feed use are approved by Health Canada and listed in the Canadian Compendium of Medicated Ingredients Brochure (CMIB). Only drugs and drug combinations that are specifically listed in the CMIB may be used in feed unless accompanied by a veterinary prescription. However, a drug that has only therapeutic approval and is not labelled for growth promotion cannot be used as a growth promoter, even with a veterinary prescription (Health Canada, 2002).

Each province in Canada has its own veterinary regulatory body, which regulates the professional conduct of the veterinarians in that province. Regulatory bodies have the right to regulate more restrictively, but not more leniently, the sale of federally approved drugs. Veterinarians can buy and sell veterinary drugs if they have a veterinarian-client-patient relationship (Health Canada, 2002).

There is public resistance to enacting legislation to require a veterinary prescription for the acquisition of all antimicrobials for use in food-producing animals due to the perception that this will cause increase costs. Furthermore, sale of drugs by veterinarians leads to income and can be perceived as a conflict of interest. Quebec has addressed this situation by establishing drug price ceilings (Health Canada, 2002).

Quebec has more stringent regulations than the other provinces. The sale of veterinary drugs is restricted to pharmacists and veterinary surgeons only. Some drugs may only be sold under veterinary prescription, while others may be sold in a veterinary office (Health Canada, 2002).

Health Canada (2010) has an “own use importation” policy that allows for importation of a 90-day supply of human-use drugs for personal use. This policy allows for the importation of some veterinary drugs by animal owners using a so-called “loophole” in the policy (CVMA, 2012; Health Canada, 2010). This loophole has garnered opposition from some individuals and groups who support legislative change to eliminate it (CVMA, 2012; Health Canada, 2002; Prescott and Szkotnicki, 2012).

Recently Health Canada (2014) announced its intention to work with the Canadian Animal Health Institute and other stakeholders to remove growth promotion and/or production claims of medically important antimicrobial drugs and to develop options to strengthen the veterinary oversight of antimicrobial use in food animals.

Several countries have implemented antimicrobial use monitoring programs, based on veterinary records or annual drug sales (Menéndez Gonzáles et al., 2010) and in the UK, there exists a five year antimicrobial strategy (UK Department of Health, 2013). Additionally, the European Union (EU) formally banned sub-therapeutic use of antimicrobials in 2006 (Raymond et al., 2006). This action has trade consequences for countries that allow the use of sub-therapeutic antimicrobials, as their products can no longer be exported to Europe (Castanon, 2007). In Ireland, the ban on antibiotic growth promotants in the beef industry has led to changes in husbandry including increased uptake of total mixed ration feeding, increased attention being paid to rumen health and the use of live yeast cultures (Hess, 2014).

The US Food and Drug Administration (2013) views the administration of medically important antimicrobial drugs to entire herds or flocks of food-producing animals for production purposes as a use that poses a higher risk to public health than the administration of such drugs to individual animals or targeted groups of animals to prevent, control, or treat specific diseases. The use of antimicrobials in food-producing animals is recognized by Canadian veterinary leaders as an area requiring a coordinated all-species, all-sector strategy to ensure prudent use and veterinary stewardship (CVMA, 2014).

There is some evidence that banning sub-therapeutic antimicrobials can cause a spike in therapeutic use to treat infections (Grave et al., 2006), which reinforces the importance of good animal husbandry to limit disease transmission (Morley et al., 2005). Disease monitoring initiatives are used in Canada to anticipate outbreaks of highly infectious diseases, one example being Porcine Reproductive and Respiratory Syndrome (PRRS). These programs can be used to implement rapid responses to decrease morbidity and mortality (Amezcua et al., 2013). It is possible to “test” different scenarios through mathematical modelling. Some studies have used modelling to predict emergence of resistance in bacteria based on different treatment protocols (Cox & Popken, 2006; Abatih et al., 2009).

Enactment of restrictive legislation can reduce overall use of antimicrobials. A study on prescribing practices in Denmark, Norway and Sweden has shown a substantial decrease in use, despite initial increases in therapeutic prescriptions. However, this study only looked at the quantities and not at the category of drugs being chosen (Grave et al., 2006). As such, this decrease in use might not be beneficial if, in fact, higher category drugs are being used more. The effects of the legislated ban on microbial populations remain to be seen (Álvarez-Fernández et al., 2012).

The World Organization for Animal Health (OIE) has outlined numerous recommendations to address the issue of AMR on a global scale utilizing collaboration on changes including legislative, regulatory, and educational (OIE, 2013). In Quebec, all veterinarians are now required to participate in a minimum of 6 hours of continuing education on the prudent use of antimicrobials prior to March 31, 2015.

In addition to legislated restrictions, voluntary guidelines have been published which advocate for the judicious use of antimicrobials by veterinarians (Guardabass et al., 2008) and support the need to use as much as necessary and as little as possible (British Veterinary Association, 2009). Some guidelines established for veterinarians are production category or species specific (AVMA(a); AVMA(b); AVMA(c); CVMA, 2008; and CVMA, 2009). As well, the Food and Drug Administration (2013) in the US has published voluntary guidelines for use of antimicrobials in food-producing animal practice.

Production Category Specific Considerations

Beef Cattle

Raising beef cattle from birth to market age involves periods of relatively little intervention, and periods of intense management. On cow-calf operations, animals generally live on pasture and disease rates are low (Green et al., 2010), and antimicrobial therapy is rarely used (Gow & Waldner, 2009). By contrast, feedlot animals are housed at high densities with intense management and morbidity in newly received feedlot calves may be as high as 40-50% (Green et al., 2010).

Prolonged periods of stress cause immune suppression (Carroll & Forsberg, 2007). Feedlot cattle are subjected to many stressors including long-distance shipping, heat or cold, social upheaval, high stocking densities and surgical procedures, such as castration and dehorning (Carroll & Forsberg, 2007). This is an abrupt transition from life as a grazing animal with minimal human handling. This transition leaves animals vulnerable to infectious diseases, which they are exposed to through mixing with animals from different sources (Nickell & White, 2010).

The major disease affecting stocker and feedlot cattle is Bovine Respiratory Disease (BRD), which is multi-factorial with many different causal organisms. Most of these organisms are normal inhabitants of the upper respiratory tract that have proliferated. Furthermore, these organisms may change in relative importance during the progression of the disease (Stanton et al., 2010). This situation makes it challenging to screen newly arrived cattle, particularly since they may not show outward signs of illness (Gonzáles-Martín et al., 2011).

Since beef cattle usually change ownership at least once during their path to market, feedlot managers may have little or no information on the health status of the animals. As well, the varied sources of animals make it difficult to ensure consistent health management throughout their life (Nickell & White, 2010). A recent report suggests that 83% of US feedlot cattle receive treatments of antimicrobials through feed or water, or by systemic administration (Carson, 2010). Many feedlots make use of metaphylactic treatments with antimicrobial pharmaceuticals, such as tetracycline, florfenicol, tilmicosin, tulathromycin and tildipirosin. This approach is based upon the assumption that the animals in the group are either susceptible or are already harbouring disease (Gonzáles-Martín et al., 2011).

Some of the most commonly used oral medications are tylosin and tetracyclines (Carson, 2010). Sub-therapeutic tylosin acts as a growth promoter (Kim et al., 2012), as well as a prophylactic treatment against liver abscesses (Inglis et al., 2005). Drugs in the tetracycline family can promote growth and prevent liver abscess, diarrhea, foot rot and BRD (Inglis et al., 2005). The vast majority of drugs used in beef cattle are lower-priority agents such as ionophores, with less than 1% of medications from Category I (Carson et al., 2008). However, there are some therapeutic applications for Category I drugs. For example, ceftiofur is used in treating BRD, foot rot, and post-partum metritis (Carson, 2010). Additionally, off-label usage is recommended to treat neonatal septicaemia and enteritis (Carson, 2010).

The link between antimicrobial use and resistance in beef cattle has been actively examined, with very conflicting results. Several studies have found little or no association between medication use and bacterial resistance (Alexander et al., 2010; Rao et al., 2010; Morley et al., 2011). Other studies have found a strong link, including one that looked at calves with neonatal enteritis. Calves that were treated with penicillins, streptomycin or tetracyclines were much more likely to shed antibiotic-resistant *E. coli* in feces (Gibbons et al., 2014). This has also been observed in adult animals, whereby cows with a history of tetracycline treatment shed tetracycline-resistant Campylobacter (Inglis et al., 2005) and *E. coli* (Alexander et al., 2010) in feces.

A study on tetracycline-resistance genes in wastewater lagoons found higher levels in feedlots with heavy medication use (Peak et al., 2007), reinforcing the finding that sub-therapeutic antimicrobials exert selective pressure on intestinal microflora. In another study, researchers at an abattoir were able to isolate ampicillin and tetracycline-resistant *E. coli* on 100% of animals examined (Alexander et al., 2010). Although the animals on antimicrobial growth promoters had higher fecal counts of resistant bacteria, there was no difference seen in the hides and carcasses of the two groups (Alexander et al., 2010). There are many other factors that impact fecal shedding of bacteria, including environmental sources, nutrition (Shanks et al., 2011) and seasonal changes (Morley et al., 2011).

Dairy Cattle

Introduction

The dairy industry is becoming increasingly industrialized, and the veterinarian's role in the industry is constantly evolving (Leblanc et al., 2006). Over the past several decades, average herd sizes have become larger and average milk production per cow has increased by over 50% in the US (Hill et al., 2009). This creates new challenges in herd health management, as cows are housed at higher densities and are placed under greater metabolic stress (Leblanc et al., 2006). As milk production increases, there is a corresponding increase in production-related diseases, which impact negatively on food quality and animal welfare (Trevisi et al., 2014). Unlike in the poultry, swine and beef industries, the majority of antimicrobial drugs used in the dairy industry are for therapeutic purposes (Leblanc et al., 2006). Antibiotics are key components of the treatment regimen for common diseases including mastitis, lameness, respiratory disease and gastrointestinal disorders (Sawant et al., 2005). There are prophylactic uses of antimicrobials in the dairy industry as well, such as dry cow therapy (Zwald et al., 2004) and use in foot bath disinfection programs. Routine practices vary worldwide based on cultural and legislative differences affecting food safety, access to drugs, and different modes of dairy production (Bennedsgaard et al., 2010).

Research on antibiotic use on dairy farms in North America is rare. Friedman et al., (2007) reported on a pilot project on farmers' knowledge, attitudes and practices related to antimicrobial use in dairy herds in South Carolina. Although few producers used written protocols, all participants determined the need for antibiotic use on a symptom based assessment and used veterinarians as their information source about antibiotics. In another report, the extra-label intramammary use of drugs in dairy cattle was studied (Smith et al., 2005). It was found that intramammary extra-label drug use was frequent, often with little available information on pharmacokinetics, withdrawal times and efficacy.

For the purposes of this review, antimicrobial use in dairy cattle will be considered under the following production categories: lactating cows, dry period, and replacement heifers.

Lactating Cows

Mastitis is the most common disease in lactating dairy cattle (Thomson et al., 2008; Hill et al., 2009), and causes significant economic losses (LeBlanc et al., 2006). Mastitis can be caused by intramammary infections, trauma, or chemical insults. Infectious mastitis can be categorized as clinical or subclinical based on clinical signs and milk composition (Barlow, 2011). Milk quality is negatively impacted by an increase in somatic cell count (SCC) and both clinical and subclinical mastitis can impact milk production and quality (Lam et al., 2013). Most published recommendations suggest basing treatment decisions on clinical signs, as well as using culture and sensitivity results to select an appropriate therapeutic protocol for the causative organism (Roberson, 2003; CVMA, 2008). Some forms of chronic mastitis, including those caused by *S. aureus*, respond poorly to antimicrobial therapy (Bennedsgaard et al., 2010). A survey of Wisconsin farmers found that cephapirin (a first generation cephalosporin), pirlimycin (lincosamide), and amoxicillin (beta-lactam) were the preferred intramammary treatments for clinical mastitis (Pol & Ruegg, 2007). Common parenteral treatments included penicillin, tetracycline and ceftiofur (Pol & Ruegg, 2007).

Causative organisms of mastitis are generally classified as environmental or contagious. Changes in housing and management systems may result in an increase in environmental mastitis. These infections, often caused by *E. coli* and other coliforms, are usually self-limiting in duration, and may not require antimicrobial therapy. Bacteriological culture of milk samples often result in no growth of causative organisms. Generally speaking, supportive care is sufficient for successful resolution of these clinical cases, and antimicrobial therapy is not necessary (Roberson, 2003). Recently, on-farm culture systems have been developed and evaluated in order to select clinical cases that appropriately require antimicrobial treatment. Lago et al. (2011(a)) reported an overall reduction in antibiotic use and milk withholding with the use of an on-farm culture system to select gram-positive clinical mastitis cases for antimicrobial therapy. Furthermore, the on-farm culture based therapy protocol resulted in similar milk production, SCC, risk of mastitis recurrence and cow survival (Lago et al., 2011(b)).

Dry Period

There is evidence that the modern high-yielding dairy cow is more susceptible to infectious diseases, particularly during the transition period when lactation resumes (Trevisi et al., 2014). Successful management of the transition cow involves nutritional support (Zwald et al., 2004), minimizing environmental stress (Trevisi et al., 2014) and often the use of dry cow therapy (DCT) (Bennedsgaard et al., 2010). DCT is an infusion of specifically formulated, long acting intramammary antimicrobials at dry-off to treat existing intramammary infections and prevent new mastitis infections (Raymond et al., 2006). DCT is widely recommended (NMC, 2009), and it is routinely used in conventional US dairy farms, with 75% of producers using so-called “blanket” treatments, where all cows are treated, at dry-off (Hill et al., 2009). DCT products are available over-the-counter in many jurisdictions (Hill et al., 2009). These products usually consist of penicillins or aminoglycosides (Menéndez Gonzáles et al., 2010). Another option for the prevention of new intramammary infections in the dry period is the use of teat sealants at dry off (Raymond et al., 2006). DCT can reduce the incidence of mastitis early in lactation (Hill et al., 2009), and it does not appear to contribute to AMR (Menéndez Gonzáles et al., 2010).

While blanket DCT has been a cornerstone of comprehensive mastitis control programs, it is clear that reduction in the overall use of antimicrobial pharmaceuticals in the dairy industry will need to involve reduced use of blanket DCT. Recently, Scherpenzeel (2014) reported on the use of selective DCT in cows with low SCC, using a split udder design. While there was an increase in SCC and clinical mastitis in non-treated quarters after calving, the total antibiotic use related to mastitis was reduced by 85% in these quarters. In other recent research, an evaluation of selective DCT based upon on-farm milk culture reported that significant reductions in dry cow antibiotic could be achieved without an increase in intramammary infection at calving (Cameron et al., 2014). Furthermore, the economic sustainability of this method was attractive (Cameron and Keefe, 2014).

It is noteworthy that studies have found that up to 50% of quarters of primiparous heifers are infected before the first calving. As such, there could be a long-term benefit from early intervention with antibiotics. However, this approach is only beneficial on farms where background mastitis rates are high (Borm et al., 2006).

It is also important to note that DCT is not permitted in USDA-approved organic farming (Zwald et al., 2004). However, DCT can be used in limited circumstances in organic production systems in Europe (Thomson et al., 2008; Bennedsgaard et al., 2010). Thus, organic dairy producers need to manage dry cows differently. Organic farms use a variety of non-pharmaceutical products via oral or intramammary administration. These include whey products, garlic tincture and vitamin C (Pol & Ruegg, 2007).

Replacement Heifers

The conditions under which replacement heifers are raised can have a significant impact on their future health and productivity (Trevisi et al., 2014). Heifers have traditionally been raised on the farm of origin, but increasingly farmers are choosing to ship their calves to specialized contract heifer-raising facilities (Walker et al., 2012). Commercial heifer facilities have many advantages. For example, they tend to have good biosecurity protocols, and their personnel can spend relatively more time on disease prevention (Stanton et al., 2013). However, there are disadvantages associated with the transportation and co-mingling of animals from different sources, including environmental, social and nutritional stresses (Stanton et al., 2010). This situation is somewhat comparable to the movement of beef cattle to a feedlot (Stanton et al., 2013). Heifer ranches may feed milk replacer with added antimicrobials, often a formula of tetracycline and neomycin (Sawant et al., 2005). In the US, 57.5% of pre-weaned heifers receive medicated milk replacer (Berge et al., 2009). Heifers raised in their home dairy are more likely to receive whole milk (Berge et al., 2005), which is beneficial in reducing diarrhea, but should be pasteurized to reduce the risk of harmful infections (Walker et al., 2012).

The primary indications for antimicrobial therapy in replacement heifers are respiratory disease and diarrhea (Ortman & Svensson, 2004). Diarrhea is the leading cause of mortality in pre-weaned calves (Berge et al., 2009), and it is commonly treated with ceftiofur (Raymond et al., 2006). For weaned heifers, the primary indication is respiratory disease (Stanton et al., 2012), which is often treated with florfenicol, tilmicosin or ceftiofur (Raymond et al., 2006).

Poultry

Several different species of birds are raised for agricultural products, including chickens, turkeys, ducks and game birds such as quail (Agunos et al., 2013). Poultry products, including eggs and meat, are important sources of affordable animal protein worldwide (Hughes et al., 2008). They are a critical source of food and income for developing nations in Africa and Asia (Sirdar et al., 2012; Kodimalar et al., 2014). Per capita chicken consumption continues to increase in the US, leading to consolidated, highly industrialized production systems to keep costs down (Jacob et al., 2008). Broiler production has been described as one of the most intensive forms of animal husbandry (Hughes et al., 2008), with animals being housed at very high densities in all stages of production (Álvarez-Fernández et al., 2012). This approach can facilitate the spread of pathogens, including those with zoonotic potential such as Salmonella (Álvarez-Fernández et al., 2012). The poultry industry is heavily dependent on the use of antimicrobials to control the spread of disease (Sirdar et al., 2012), to promote weight gain in meat birds (Singer & Hofacre, 2006), and to improve performance in layers (Kodimalar et al., 2014). Antimicrobials in poultry can be used at therapeutic or sub-therapeutic doses, and a wide variety of treatment protocols have been described (Chapman and Johnson, 2002).

Low-dose antimicrobials are used to increase growth rates and improve feed efficiency (Huyghebaert et al., 2010). In 1995, this usage accounted for 42% of veterinary antimicrobial usage in poultry worldwide, with therapeutic applications trailing at 18% (Kodimalar et al., 2014). The increasing popularity of growth promoters is also believed to be the primary cause of an observed 300% increase in antimicrobial usage on conventional poultry farms during the 80’s and 90’s (Sapkota et al., 2011; Gyles, 2008; Schwaiger et al., 2008). The mechanisms by which antimicrobials increase growth rate and food efficiency are not entirely understood, but it is clear that they alter the composition of the intestinal microbiome, which is intimately linked to host immune status (Lee et al., 2012). Some possible mechanisms for the improvement of performance include clearance of subclinical infections or elimination of microbial competition for nutrients (Huyghebaert et al., 2010). Additionally, antimicrobial growth promoters cause the intestinal walls to thin, which could permit greater nutrient absorption (Huyghebaert et al., 2010). Concern about the development of AMR led the European Union to ban the use of antibiotics as growth promoters in 2006 (Singer & Hofacre, 2006), and public perception of these risks has created an increased demand for antibiotic-free poultry in North America (Jacob et al., 2008).

Alternative growth promoters are an area of active research; some options include prebiotics and probiotics (Hume, 2011), essential oils, and immune-stimulants (Huyghebaert et al., 2010). It was recently demonstrated that bee pollen has prebiotic properties when used as a food additive (Kačániová et al., 2013). Currently up to 88% of broilers in the US receive roxarsone, an organoarsenic compound. It promotes weight gain and improved feed efficiency, and also acts as a coccidiostat when combined with an ionophore (Chapman & Johnson, 2002; Lee et al., 2012). Roxarsone is more cost-effective than antibiotics and could encourage decreased antimicrobial usage (Chapman & Johnson, 2002). However, arsenic can accumulate in tissues such as feathers, which may find their way back into the human food system in the form of fertilizer or by-products in feed (Nachman et al., 2011).

The primary infectious problems affecting poultry are gastrointestinal and respiratory diseases (Hughes et al., 2008). Intestinal infections, such as colibacillosis and necrotic enteritis, are the primary indicator for antimicrobial therapy (Rosengren et al., 2009; Geier et al., 2010). In terms of respiratory infections, *E. coli* is the most significant causative organism and is often secondary to a different infectious or environmental stress (Singer & Hofacre, 2006).

Similar to the situation that exists in the small ruminant sector, there are few medications licensed for use in poultry, particularly the minor species such as game birds (Agunos et al., 2013). A survey of American poultry producers found that 42.4% had used therapeutic prescription antibiotics in the previous year, with amoxicillin, (an extended-spectrum penicillin) and tylosin (a macrolide) being the most widely used medications. Lincosamides were used both preventively and therapeutically (Hughes et al., 2008). Ceftiofur is widely used in Canada as a prophylactic in ovo injection (Webster, 2009). This is a controversial extra-label usage, since ceftiofur is a Category I drug which is not licensed for use in avian species (Agunos et al., 2013). Its usage in poultry has been linked to the emergence of cephalosporin-resistant strains of Salmonella (Webster, 2009). Some examples of commonly used growth promoters are tetracyclines and bacitracin (Singer & Hofacre, 2006). There is some overlap between drugs used for sub-therapeutic and therapeutic purposes (Hughes et al., 2008), but given the limited number of drugs approved for therapeutic use in poultry, many American producers select different classes of drugs for growth promotion (Singer & Hofacre, 2006).

Producers in the developing world rely heavily on antimicrobials to prevent and control disease (Sirdar et al., 2012), but few studies exist documenting rates of usage (Na lamping et al., 2007). A study in Sudan found that antimicrobial products are widely available without a prescription, and producers frequently lack education on antimicrobials including withdrawal times and the potential human health impacts (Sirdar et al., 2012). Chickens are preferred protein sources for low-income countries because they require little space (Kodimalar et al., 2014); this means that poultry often live in close proximity with human households, increasing the risk of zoonotic infection. In many countries, there is little or no government oversight when it comes to disease control strategies or food safety (Sirdar et al., 2012).

Small Ruminants

Small ruminants are farmed for several different products, including milk, meat and wool. In Canada, most sheep have traditionally been raised with meat as the primary product (Avery et al., 2008). Spain and Italy have thriving sheep dairy industries, with much of the product going towards raw milk cheeses (Molina et al., 2003; Moroni et al., 2005). Some breeds of sheep, such as the Awassi sheep of Jordan, may be used for multiple purposes (Hawari et al., 2014).

There is very little data on antimicrobial usage in small ruminants (Avery et al., 2008). In fact, it appears that Norway is the only country with an active monitoring system for drug use in sheep (Scott & Menzies, 2011). The CVMA's Antimicrobial Prudent Use Guidelines do not address the subject of small ruminants (CVMA, 2008). In sheep, antimicrobials are used to treat mastitis, respiratory problems, lameness, neonatal scours, and post-lambing treatments (Avery et al., 2008). Goats have similar indications and usage patterns. Contagious agalactia is a significant health issue in European dairy goats, and is linked to mastitis, pneumonia and spontaneous abortions (Paterna et al., 2013).

There are few licensed drugs for sheep and goats. As such, extra-label drug use is an essential aspect of small ruminant practice (Mavrogianni et al., 2011). It would appear that pharmaceutical companies rely on practitioners promoting extra label use (Fajt, 2011). Extra-label drug use can be problematic because the safety and efficacy of a product is not documented (Moon et al., 2011). Dosing must be estimated, and withdrawal times have not been adequately studied in sheep and goats, increasing the risk of residues entering the food system (Pengov & Kirbis, 2009). Drug residues not only pose a public health risk but can also interfere in cheese making (Molina et al., 2003).

Antibiotic use in small ruminants is believed to be low overall (Scott & Menzies, 2011), although these findings vary with local practices. Dairy ewes and does in Europe may be managed intensively (Molina, et al., 2003), whereas meat sheep in Australia are kept on extensive grasslands and are rarely medicated (Scott & Menzies, 2011). A study of antimicrobial use in Alberta sheep farms found that metaphylactic use is rare among sheep farmers, with the majority of antimicrobials being administered by injection for therapeutic purposes (Avery et al., 2008). The most common injectable medications were penicillins and tetracyclines (Avery et al., 2008; Moon et al., 2010). In addition, tetracycline was the most common in-feed medication (Moon et al., 2011). AMR has been documented, although no causal link has been established between antimicrobial use and the presence of resistant strains (Scott et al., 2012; Lazou et al., 2014). Resistance to tetracyclines has been reported in Campylobacter species isolated from ovine and caprine GI tracts (Cortés et al., 2006). As well, beta-lactam resistant strains of Staphylococcus have been isolated from sheep and goat milk in Europe and Asia (Virdis et al., 2010; Hawari et al., 2014). This may have clinical relevance for goats, as penicillin is often used in goats for treating subclinical mastitis caused by *S. aureus* (Moroni et al., 2005).

Mastitis is a significant health issue in both meat and dairy animals. Mastitis in small ruminants is normally subclinical (Spanu et al., 2011) and the prevalence may be as high as 35% in dairy goats (Doğruer et al., 2010). Depending on the causative organism, mastitis does not necessarily decrease milk yields in goats (Koop et al., 2010). However, mastitis is known to impact milk quality by increasing the SCC (Molina et al., 2003). High SCC in milk has been linked to an increase in antibiotic residue violations, implying a history of failed treatments (Gonzalo et al., 2010). Although small ruminant mastitis is usually localized to one udder half, a study on European dairy goats demonstrated bilateral impairment caused by a unilateral infection. Goats with one chronically infected half were compared to controls with two healthy halves. It was discovered that milk from the controls had lower SCC than milk from either half of the infected goats, although the infected halves scored highest (Moroni et al., 2005).

Mastitis can be treated through intramammary or parenteral routes (Molina et al., 2003). Intramammary treatments may not be indicated for active infections, such as some Staphylococci which produce biofilms that inhibit product penetration (Virdis et al., 2010). Since few products are labelled for sheep, mastitis is often treated with single-dose bovine intramammary products (Pengov & Kirbis, 2009). Producers have reported halving the dosage in sheep since the mammary gland is so much smaller, but current recommendations are to use the full contents of the syringe (Mavrogianni et al., 2011). When using bovine drugs extra-label, withdrawal times should be extended. For example, studies on pharmacokinetics of antibiotics in sheep have found residues long after the indicated withdrawal time for cows has passed (Pengov & Kirbis, 2009).

As in dairy cattle, milk producers may use dry-off treatments. Given on a consistent schedule, dry treatments are associated with low SCC and bacterial counts in milk (Gonzalo et al., 2010). However, when given sporadically, the use of dry period therapy is linked with increased residue violations (Gonzalo et al., 2010). It is known that ewes with consistently high SCC milk are more likely to develop infections in future lactation cycles, so SCC could be used to target dry period therapy in these animals (Spanu et al., 2011).

Swine

Compared with other livestock industries, conventional pork production is characterized by an emphasis on biosecurity to control and prevent disease (Nöremark et al., 2010). There is also extensive use of biocides, both in the form of antimicrobial medications for animals (Callens et al., 2012) and in the disinfectants used for the facilities (Braga et al., 2013). Conventional swine operations house animals in high-density housing (Rosengren et al., 2009), which can facilitate the spread of infectious disease (van der Muelen et al., 2006). The primary health concerns in pigs are respiratory and gastro-intestinal conditions (Glass-Kaastra et al., 2013), as well as reproductive issues (Amezcua et al., 2013). Most antimicrobial medications are administered in feed for prophylactic and metaphylactic purposes (Rajić et al., 2006), as well as growth promotion where permitted (Kim et al., 2012). Administering antibiotics for growth promotion can promote AMR, since it is difficult to ensure accurate dosing (Akwar et al., 2008(a); Akwar et al., 2008(b)). Furthermore, the animals are usually on the antimicrobial feed additive for the long term (Rosengren et al., 2009). When treating infections, it is not uncommon to have poor responses (Glass-Kaastra et al., 2013). Multiple studies have found systematic misuse of antimicrobials, such as overdosing injectable medications and under-dosing oral medications (Timmerman et al., 2006; Callens et al., 2012). Some producers utilize alternatives to antimicrobials such as oregano oil (Ragland et al, 2006; Ragland et al, 2008)

Livestock producers do not necessarily keep thorough treatment records, and swine producers are no exception (Schuppers et al., 2005; Rosengren et al., 2008). As a result, it can be difficult to quantify antimicrobial use on swine farms. However, it appears that the tendency is to take a preventive approach. For example, a study in Belgian fattening pigs found that 93% of group treatments were given for prophylactic purposes, with only 7% metaphylactic treatments (Callens et al., 2012). Weaner piglets are frequently given medicated rations, as they are susceptible to infectious diseases (Keegan et al., 2005). Over 80% of US farmers use medicated starters, and these diets frequently contain multiple antimicrobials. In Canada, the most popular mixture is chlortetracycline, sulfamethazine and penicillin (Rajić et al., 2006). Drugs for therapeutic use, such as penicillin, are usually injected. However, this becomes less common as the animals approach market weight. This is partly due to the stress associated with handling large animals (Rosengren et al., 2009), and partly to reduce the likelihood of lesions that affect meat quality (Rajić et al., 2006). As a result, many farmers opt to treat the entire group initially, and continue treatment for those animals that show symptoms (Rajić et al., 2006; Casal et al., 2007). This means the overall length of treatment periods is highly variable, and it is difficult to distinguish between metaphylactic and therapeutic antimicrobial use (Chauvin et al., 2002). Category I drugs are rarely used in swine, with the exception that ceftiofur is a fairly common treatment for lameness, respiratory disease or enteric disease (Deckert et al., 2010). MRSA levels in pigs and in farm workers have been studied on conventional and antibiotic-free swine farms. Other than a cluster of positive pigs and workers in Iowa and Illinois, there was a low prevalence of MRSA (Smith et al., 2013).

Biosecurity protocols are highly variable between swine operations (Nöremark et al., 2010). These protocols can be classified as internal or external (Lambert et al., 2012). Internal biosecurity procedures are designed to minimize disease transmission within a facility, for example by isolating sick animals (Laanen et al., 2013). External biosecurity is directed at preventing new pathogens from being introduced into a facility, for example by keeping herds closed and breeding replacement animals on-site (Bottoms et al., 2013). Internal and external biosecurity needs can be in direct conflict. As an example, in some Québec swine units, pigs in different production stages are housed at separate facilities. This approach could enhance internal security for breeding facilities, but compromise external security in the older stages by bringing pigs from different sources together. Such a production system also permits the regional spread of disease, particularly in regions with a dense porcine population (Lambert et al., 2012).

There are various risk-based tools available to quantify biosecurity (Bottoms et al., 2013; Laanen et al., 2013). High overall biosecurity scores have been found to correlate with increased daily weight gain and favourable feed conversion ratios in pigs (Laanen et al., 2013). Additionally, herds with higher biosecurity scores make less use of blanket prophylactic treatment regimes, and high internal scores correlate with a reduced incidence of disease treatments (Laanen et al., 2013). For example, a study on fecal microbiome observed that farms with all-in-all-out production systems harbour fewer multi-resistant Campylobacter strains (Schuppers et al., 2005). In many ways, biosecurity can be considered a proxy for good management and a key area for intervention (Lambert et al., 2012).

Veal Calves

Veal production is intimately linked to the dairy industry, as most bull calves born on dairy farms are destined to become veal (Berge et al., 2006). Calves are shipped to dedicated “fattening facilities” (Bos et al., 2012) and weaned at 50-70 days of age (Berge et al., 2006). White veal is the term used for meat from a 6-8 month old, non-ruminating calf, whereas rose or red veal refers to older (8-12 month) calves that have been given roughage and concentrate to promote rumen development (Bos et al., 2012). As in replacement heifers, the stress of shipping calves, combined with the exposure to animals from many different sources, creates a population that is highly susceptible to infectious diseases (Timmerman et al., 2005). The strongest predictor of calf health is proper management of colostrum (Berge et al., 2005). This includes testing colostrum Ig levels, ensuring the calf is given a sufficient quantity within 12 hours of birth and then testing the serum Ig level of the calf. Failure of passive transfer is associated with respiratory and gastrointestinal disease, the two most common ailments in calves (Raymond et al., 2006).

To combat the stresses faced early in life, antimicrobials such as tetracycline and neomycin are often added to calf milk replacer (Berge et al., 2006). This practice can delay morbidity and decrease mortality (Berge et al., 2005), as well as promote increased growth and improved feed efficiency (Berge et al., 2009). European facilities often give blanket "start treatments" to newly arriving calves. This practice is contentious due to the link between antimicrobial usage and diarrhea (Ortman & Svensson, 2004). Almost 25% of dairy calves are affected by diarrhea before weaning (Stanton et al., 2013), making it the number one cause of morbidity and mortality (Timmerman et al., 2005). Antimicrobial therapies may cause diarrhea through disruptions of the normal intestinal biome (Berge et al., 2009). The normal biome is likely compromised to begin with, since calves are unable to pick up beneficial microbes from their dam due to early separation (Timmerman et al., 2005). Diarrhea is often treated with antimicrobials such as ceftiofur and sulfa/trimethoprim (Raymond et al., 2006). Even if the cause of the diarrhea is not bacterial, it is possible that antimicrobial therapy is warranted, as secondary *E. coli* overgrowth may develop in the small intestine (Berge et al., 2009). However, most drug therapy for mild diarrhea is not beneficial and, in fact, antibiotic treatment may be associated with higher mortality (Ortman & Svensson, 2004).

Bovine respiratory disease (BRD) is the other major reason for antimicrobial treatment in veal production. That said, very little research has been conducted in this area, as compared to beef feedlot production systems. Rerat et al. (2012) has reported on an evaluation of the efficacy of two prophylactic antibiotic treatments against BRD in veal calves. Improved performance attributed to a lower incidence of BRD in the first days after arrival was found in the prophylactically treated animals.

A study of European production animal systems found substantial levels of AMR in veal units (Pardon et al., 2012), indicating that veal farms could be a key target for AMR risk-reduction strategies. It has been demonstrated that veal producers, their families and employees have a substantially higher risk of colonization by methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA is rare in the general population, with an estimated prevalence of less than 1% in Holland. By contrast, 33% of Dutch veal producers are MRSA carriers at a given time, and these organisms appear to be passed directly from animals to humans (Graveland et al., 2010). Veal farmers are at risk of developing MRSA-infected wounds if they cut or injure themselves, in addition to presenting a public health risk. Ensuring proper farm hygiene and avoiding unnecessary antimicrobial use can reduce the risk of MRSA infections (Graveland et al., 2010).

Conclusion

From this review of selected published literature, legislation and guidelines related to the use of antimicrobial pharmaceuticals in food-producing animal production systems over approximately the last 10 years, as of July 2014, it is clear that the use of antimicrobial pharmaceuticals is a prominent aspect of food-producing animal production systems. Antimicrobial pharmaceuticals are used in the treatment and prevention of infectious disease, and sub-therapeutically to promote rapid growth and increase feed efficiency. Formal evaluations of a wide array of antimicrobial therapy programs in a variety of food-animal species have become increasingly prevalent in the literature. On the other hand, reports that document the attitudes and practices of producers, veterinarians, and industry leaders are quite rare.

From this review, it is also noteworthy that the development of regulatory controls and guidelines are increasingly focused on monitoring and slowing the development of AMR in various food-animal production systems, as well as promoting the adoption of practices that are sustainable while protecting the human population.

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