From Cows to People and Back Again: Antimicrobial Resistance Risks and Stewardship

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Introduction

For several decades the use of antimicrobials (AM) in food animal production has been touted as a major risk for the development of antimicrobial resistance (AMR) in human pathogens. As early as 1970, consumer groups asked the U.S. FDA to remove antimicrobials used for growth promotion in food animals (Kahn, 2016) but this was not done in the U.S. until the Veterinary Feed Directive went into effect on January 1, 2017. This paper will share some of the recent risk assessments for the claim that food animal antimicrobial use (AMU) is a problem, highlight current antimicrobial uses in dairy cattle, risks for AMR, and focus on areas for improvement of antimicrobial stewardship in the dairy industry.

Risks

There is really no debate that AMU can drive AMR in dairy cattle or people. The debate is over the actual risk that AMR in human pathogens is derived in part or wholly from AMU in food animal agriculture, i.e. is there a risk for horizontal transmission of genes encoding for AMR from animal-derived bacteria to human pathogens? There are over 10,000 pages of PUBMED entries for 'antimicrobial resistance', books written on the topic, and multiple millions of hits in an internet search just for "AMR and dairy". The story is complicated because not only does AMU affect AMR, there can be selective pressure by metals, disinfectants, or biocides (Thanner et al., 2016). There are also multiple mechanisms and multiple genes responsible for AMR, making the study of it even more complicated. In addition, the sequence of when and where a particular type of resistance originated is complicated. For example, Davis et al. (2015) described the emergence of AMR *E coli* with the bla CTX-M gene conferring resistance to cephalosporins. Evidence pointed to emergence of this resistance gene in people several years before it was seen in dairy cattle in Washington State.

In a review paper from the Harvard School of Public Health, Chang et al. (2015) highlighted the agriculture antibiotic controversy and the ways in which people could obtain AMR bacteria through AMU in food animals. Although the authors believed that AMU in agriculture posed a threat, they felt that the extent of the problem may be exaggerated and that agriculture is not largely to blame, that AMU in human medicine posed a much bigger risk and that "the evidence for human health risks directly attributable to agricultural antibiotics runs the gamut from speculative to scant." A Canadian group reported on a systematic review of reducing AMU in food animals and subsequent reduction in AMR in animals and people (Tang et al., 2017).

Restricting AMU in animals resulted in a pooled risk reduction of AMR in animals between 10 to 15%. They concluded that reduction in AMU in animals was associated with a reduction in AMR in people, particularly farm workers. This review covered many study species: beef cattle, dairy cattle, poultry (broilers, turkeys and egg layers), swine, goats, and salmon. Their conclusions were that the evidence was consistent and substantial that reduction of AMU in animals could reduce AMR in animals and people.

An Australian group published a systematic review and found that "Limiting antimicrobial use in food animals reduces antimicrobial resistance in food animals, and probably reduces antimicrobial resistance in humans. The magnitude of the effect cannot be quantified" (Scott et al., 2018). From an extensive review of AMR in dairy cattle by Burgess and French (2017) in New Zealand: "Although there is limited evidence for the transmission of antimicrobial resistant bacteria and their genes between dairy cattle and humans, it is clear that antimicrobial use can lead to bacteria in the gut of dairy cattle developing AMR."

The risk to animals and humans and back again depends on many things and is complicated. The first report of methicillin- resistant *Staphylococcus aureus* (MRSA) transmission on a dairy farm was reported by Juhasz-Kaszanyitzky et al. (2007) in Hungary. There were multiple MRSA infections in the mammary glands of cows and carriage of a similar type in a farm worker. The authors could not, however, conclude which direction the transmission went. Researchers investigating staphylococcal populations responsible for causing mastitis in dairy cows in South Africa found that humans carried more antibiotic-resistant staphylococci than the farm animals with which they worked (Schmidt et al., 2015). This diversity seen in people is likely an indication that their origins are in people in this study. About 10% of sporadic MRSA infections in people in Europe are associated with livestock, particularly swine, and some strains of MRSA appear to have jumped from people to dairy cattle and back (Cuny et. al, 2015). In the U.S., the evidence for sharing AMR isolates is primarily from swine operations (Smith, 2015). In Europe, less than 2% of human clinical MRSA isolates were attributed to livestock-associated MRSA despite high carriage of MRSA in livestock (van Cleef et al., 2011). Although there are no clear pathways fro transmission, the potential for AMR to move from people to cows and back again exists.

<u>AMU in Dairy</u>

For dairy cattle, the most common AMU is to treat mastitis and for dry cow therapy. In a 2011 review, Oliver et al. examined the evidence for AMR from AMU in dairy cattle. For mastitis pathogens, the evidence was still murky and depended on the bacterial species. The story may be different for systemic AMU and fecal *E coli* with the conclusion that these bacteria can serve as reservoirs for AMR genes but that multidrug resistance may be transient in treated cows.

Dry Cow Therapy (DCT) has been a cornerstone of mastitis control recommended by the National Mastitis Council. Because of the total amount of drug being used with blanket DCT, alternatives to this practice have been considered and some investigated. Results of these investigations appear to be mixed. Despite this, most countries have called for a shift from blanket antimicrobial DCT to selective DCT based on the risk of infection from the cow's history, last somatic cell count (SCC) test results, or milk cultures. Suggestions from the UK are to use an internal teat sealant on all cows and selectively treat high risk cows (Biggs et al., 2016). The Netherlands changed from blanket DCT to selective DCT at the end of 2012 (Vanhoudt et al., 2017). Over the subsequent years a subset of herds were monitored. This policy led to a dramatic reduction in AMU and did not appear to significantly increase new IMI or mean percent cured IMI during the dry period. It should be noted that the Dutch-recommended pre-dry off SCC levels to trigger antimicrobial DCT were 150,000 cells/mL for primiparous cows and 50,000 cells/mL for multiparous cows, much lower than the 200,000 cells/ml suggested elsewhere (Vissio et al., 2014).

Therapeutic AMU is conventionally based on clinical signs of mastitis. Intramammary therapies are primarily for specific, contagious pathogens, but with the reduction in those contagious pathogens in the U.S., farmers are left with mostly environmental pathogens for which there may not be label claims. For a review of mastitis therapy, see Ruegg (2018). Other, major uses of antimicrobials are for the treatment of metritis and lameness in dairy cattle.

AMU in calves is an area of great concern because of the widespread use as well as the often lack of evidence for effective treatment of conditions such as diarrhea with AM. Treatments on large farms are in the hands of employees who likely have variable levels of training on AMU. In addition, because there are few label claims for non-ruminating animals for these drugs, extra-label drug use is required. Overuse of AM in calves is common because of the "need to do something" but actually may cause harm because of antibiotic-associated diarrhea (Berge et al., 2009). Farm personnel may not be responding to the same clinical cues that a veterinarian might (Moore et al., 2015) and may base their treatment decisions on personal beliefs and values (Crudo et al., 2016).

Several studies have evaluated the use of non-saleable (waste or hospital) or medicated milk for calves and the increase in AMR fecal *E coli*. Non-saleable milk may have measureable levels of antibiotics as well as AMR bacteria (Tempini et al., 2018). In a report to the European Commission, Ricci and others (EFSA, 2016) reviewed data and literature on AMR in milk-fed calves. They concluded that low concentrations of AM select for resistance and that low AM concentrations in waste milk from treated cows poses a risk to AMR development in calf intestinal microbiota. However, based on some of our work (Moore et al., 2012) and others (Foutz et al., 2018), the multidrug AMR appears to be transient if calves receive medicated milk replacer or non-saleable milk.

What if AM were not available or therapy was restricted to alternatives? In an economic model from Cornell, those questions were addressed (Lhemie et al., 2018). Total restriction of AMU and alternative treatments had costs per cow per year associated with these strategies of $150 and $61, respectively, and through a sensitivity analysis, major drivers of that cost included replacement animal costs, milk price and slaughter price. One scenario looked at increasing the cost of AM to discourage use. The cost would have to be five times that of current prices to outweigh the benefits from AMU.

AMR and the Environment – The Global Resistome

Human and animal bodies are microbial ecosystems. Soil is also a microbial ecosystem. Antibiotics are naturally made by fungi and bacteria for their survival in the environment. However, antibiotic concentration levels produced by environmental bacteria are often far below therapeutic doses suggesting that AM produced by bacteria may serve some other function (Berglund, 2015). The genes for resistance in bacteria are all around us: in wastewater, manure, and farm fields, and birds and rodents and people help to move the genes around. There is evidence that wildlife can sustain AMR genes in their associated bacteria or at least disseminate those (Arnold et al., 2016).

The dairy environment can serve as a reservoir of resistance genes through waste water, runoff, manure application, milk, cow to cow, cow to calf, or calf to calf. Dairy soils were more likely to have AMR genes for tetracycline and streptomycin compared to non-dairy soils (Srinivasan et al., 2008). Manure application (with intact antimicrobials or their metabolites as well as AMR bacteria from feces) is thought to be one way to 'spread' AMR. One study found that manure application (from cows not treated with antibiotics) induced a bloom of soil bacteria that were AMR (Udikovis-Kolic et al., 2014). Chamosa et al. (2017) noted that there is a large reservoir of AMR gene cassettes in environmental bacteria, these bacteria can maintain these gene cassettes at no biological cost, and eradication of AMU in a hospital or veterinary environment may not be sufficient to remove these cassettes in bacterial populations. A recent review of antibiotics and AMR genes in the environment noted that for waste water, "even a three-step (mechanical, biological, and chemical) treatment is not sufficient to remove all antibiotics" (Bloomer et al., 2018). In a modeling study, minimum local ambient temperature as well as population density were strong drivers of U.S. AMR in *E. coli*, *Klebsiella pneumonia*, and *Staph. aureus*, controlling for human prescription rate and number of outpatients (McFadden et al., 2018). We know little about the contributions that soil may make in the dissemination or perpetuation of AMR. For a concise review of knowledge gaps in AMR in plant and animal agriculture including the environment, see Thanner et al. (2016).

When it comes to AMU in dairy cattle, it's all about the people

Aarestrup (2015) summarized his thoughts on livestock as a reservoir for AMR. He outlined the positive effects of using antimicrobials for animal welfare, disease reduction, economics, increased production, cheaper food and others. The negative effects were increasing resistance and colonization with zoonotic bacteria, resistance on the farm and effects on human society. He also separated out some additional factors for the use of more antimicrobials on some farms, including tradition, the need to do something, direct measureable effects, easy management tool, insurance against disease outbreaks, poor management, and industry lobbying. The "need for something to do" and "cheap insurance" are strong motivating factors for farmers as well as their employees when using antimicrobials.

A recent paper on UK veterinarians' perceptions of selective DCT identified some of the issues they face when potentially suggesting this practice, including (1) don't change something that isn't broken, (2) difficulty engaging some clients, particularly by younger veterinarians, (3) fear of changing processes and (4) inexperience with alternatives (Higgins et al., 2017). To make alternatives to blanket DCT work, the veterinarians suggested workshops for farmers to show them how others made it work, clinical guidelines and standard operating procedures and availability of on-farm or affordable diagnostics. In New Zealand, most surveyed veterinarians believed that the risk of AMR developing in dairy cows was real but that AMU on farm was not a cause of resistance in people. Their AMU was primarily influenced by "technical factors" in addition to client feedback on perceived efficacy and cost/benefit (McDougall et al., 2017).

Jones and others (2015) investigated AMU from the UK dairy farmers' perspective. A prevalent motivator to reduce AMU was cost-savings to the farm and although 90% believed they were already engaged in good AMU practices about half were not aware of the UK *Responsible Use of Medicines in Agriculture* publication. Farmers in this study were primarily influenced by their veterinarian for farm disease control activities as were farmers surveyed in New Zealand (McDougall et al., 2017). Veterinary oversight of AMU is considered by most countries as the principle component of an antimicrobial stewardship program.

Stewardship

In September of 2018, the U.S. announced the *AMR Challenge* at the U. N. General Assembly (https://www.feedstuffs.com/news/us-challenges-world-intensify-global-fight-against-antibiotic-resistance?NL=FP-006&Issue=FP-006_20180926_FP-006_142&sfvc4en). Specifically, the suggestions were to: Reduce antibiotics and resistance in the environment (e.g., in water and soil); Improve antibiotic use, including ensuring that people can access these medicines when they are needed; Develop new vaccines, drugs and diagnostic tests; Improve infection prevention and control, and Enhance data sharing and data collection. Reduction of AMU can be equated to stewardship. Antimicrobial stewardship (AMS) is defined as a coordinated program to promote responsible use and is touted as an important component of reducing use of antimicrobials in both human and veterinary medical practice.

Veterinary organizations are developing or have developed antimicrobial stewardship (AMS) guidelines. One such set of guidelines was developed by the American Association of Bovine Practitioners (AABP) and is available on their website (http://www.aabp.org/resources/AABP_Guidelines/AntimicrobialStewardship-7.27.17.pdf). The AABP AMS program has five key elements: (1) Practice leadership commitment to AMS, (2) Drug expertise, (3) Tracking drug use in practice and on client farms, (4) Reporting back to clients, and (5) Action after monitoring that could include reviewing disease prevention programs, diagnosis and treatment protocols, and a review of drug efficacy. Although these guidelines have been circulated there is no information on implementation rates or impact of the "Five Key Elements" and no insights into the motivations and barriers to implementation by practitioners.

While there is no published information about motivations for and barriers to implementing antimicrobial stewardship programs in cattle practices in the U.S., a recent Australian study surveyed all practice types and identified: "a lack of AMS governance structures; client expectations and competition between practices; cost of microbiological testing; and lack of access to education, training and AMS resources" as key barriers to implementation. "Concern for the role of veterinary antimicrobial use in development of AMR in humans, a sense of pride in the service provided, and preparedness to change prescribing practices" were identified as key enablers (Hardefelt et al., 2018). Carmo et al. (2018) conducted a country by country European expert opinion study of potential drivers for changing antimicrobial usage practices in livestock and cited these key areas as enablers of AMS programs: use of susceptibility testing; identification of treatment failures; common diseases requiring antimicrobial treatment; policy changes; farm biosecurity; and veterinary education. It is clear from these studies that continuing education programs designed to address practice-specific enablers and barriers are still needed to promote adoption of AMS and that there are likely technical enablers for adoption of some of the elements.

Technical enablers of AMS adoption would include quick diagnostics and dairy antibiograms as well as evidence-based alternatives to antibiotics, on-farm evaluation of therapy outcomes, and easy AMU and AMR benchmarking. Dairy antibiograms would allow veterinarians to determine if antibiotic resistance to a particular treatment is present on a farm. In addition, reliable on-farm health and treatment record-keeping systems could allow for assessment of treatment efficacy. Suggestions to setting up such record-keeping systems on-farm are available at: https://vetextension.wsu.edu/research-projects/gdhr/tools/vetguide/. An AMU benchmarking tool and metrics have been proposed for cattle practice in the UK and the *Dairy Antimicrobial Usage (AMU) Calculator* was created (Mills et al., 2018).

Investigators have been evaluating alternatives to antimicrobials. Biosecurity, improving host resistance to disease and other disease prevention strategies are the first line of defense. For treatment, a number of agents have been investigated. Phage therapy has been tried for *S. aureus* and *E. coli* and *Strep. uberis* but may not be effective or lack evidence of efficacy. Phytochemicals and metals are novel antibacterials and include polypehonols and metal nanoparticles. Used alone or in combination, these agents appear to be effective against bacterial pathogens (Betts, et al., 2018). However, in a recent clinical trial, three phytoceuticals were evaluated for treatment of experimental *Strep. uberis* mastitis infections but they did not produce bacterial cures (Mullen et al., 2018). For a recent review of alternative therapies for mastitis, see Gomes (2016).

Genomic testing and selection for mastitis or other disease-resistant cows may be one alternative strategy to reduce AMU. We have been able to select low SCC bulls for some time and now have the ability to select cows for mastitis resistance and "wellness" (Weigel and Shook, 2018; Martin et al., 2018). Selection for mastitis resistance may also select for resistance to other diseases (Martin et al., 2018).

An important component of a veterinary practice AMS program would include client education. Jones and others (2015) suggested that key points to convey to farmers would include: the role that the use of antibiotics has in causing antibiotic resistance both in animal pathogens and potentially for human pathogens; advice on best practices for AMU with specific management actions or alternative treatments that would permit reductions in AMU without financial losses; data on cost savings that might be obtained from reduced antibiotic use; and assurance that there are low risks to animal welfare from reduced AMU.

Continuing education programs on AMS for both veterinarians and dairy farmers would be a start to help reduce AMU. However, implementation and making a real change requires that we have the ability to enact guidelines for stewardship. Lloyd and Page (2018) suggested that an AMS program should focus on disease prevention and control and approaches to avoid AMU. An AMS program should also include a framework for continuous improvement by reviewing where a farm is, what the program objectives are, and how to measure progress. Although directly addressing farmers' and veterinarians' education is important in the short-term, longer term strategies should include AMS education for students. The Association of American Veterinary Medical Colleges and the Association of Public & Land Grant Universities along with the Food and Agriculture Organization of the United Nations, drafted a set of core competencies for educating youth, animal science undergraduate and veterinary medical students on AMR (http://www.aavmc.org/assets/site_18/images/amr-lo-final.pdf).

Conclusions

Dr. Laura Kahn, in her book, *One Health and the Politics of Antimicrobial Resistance* (2016), summarized the goals for public health and agriculture. She said they "should be to optimize human, animal, and environmental health: in essence, One Health." Her belief is that science and technology will rally to address the challenges but that takes some time. The ultimate goals are to preserve the effectiveness of antibiotics and provide animal proteins to a growing population. We can do this through advancing real and effective antimicrobial stewardship practices throughout our industry.

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