Antibiotic Overuse in Agriculture: Implications for Animal and Human Health
A Literature Review

Capstone Project: Master's Paper

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Introduction

- Antibiotic fortified feed has been utilized in the agricultural field for over 60 years due to weight gain and disease prevention benefits.
  - Reduced mortality in young pigs by 50%
- Earlier research found that Antimicrobial Growth Promoters (AGPs) could enhance the growth and feed conversion ratio, ultimately increasing labor or capital productivity.
  - AGPs improved growth rate and feed efficiency by 4.2% and 2.2% for the entire growing and finishing period.
  - AGPs resulted in a total net return of $2.99 per pig.

Introduction Cont.

- Weight gain and economic benefits caused antibiotic sales to increase.
  - In 2014 the FDA estimated that 15.4 million kg of antibiotics were sold for animal use.
- The agricultural industry utilizes more than four times the amount of antibiotics as compared to the medical field.

Introduction Cont.

- The same antibiotics used for therapeutic purposes are also being used for growth promotion purposes.
  - Increased microbial resistance to drugs like fluoroquinolones, used for animal and human treatment, can be attributed to their use in animal feed as well as veterinary medicine.
- Excessive use of antibiotics that are important for treatment have been observed and reported in animal husbandry in recent years, leading to selection of resistant bacteria in food animals.
  - This poses health risks for animal, human and environmental health.

Purpose

The purpose of this review is not to have an all-encompassing view, but to attempt to add new perspectives on the epidemiological triad that exists between humans, animals, bacterial organisms and the environment, and how the overuse of antibiotic fortified feed impacts overall community health and what can be done to improve overall health.

Methods

- PubMed, Google Scholar and the National Institutes of Health were used to identify peer reviewed scientific articles.
- Keywords searched in combination with antibiotic resistance:
  - Agriculture
  - Food Animal
  - Manure Runoff
  - Ecological Effect
  - Transmission
  - Antibiotic Misuse

Methods Cont.

Inclusion Criteria

- Published within the last 5 years
- Full texts
- Free full texts
- Articles written or translated into English

Exclusion Criteria

- Published before 2010
- Review articles
- Sample size less than 20 participants or specimen collection less than 500

Results

- The results of 19 articles were organized based on five main topic areas identified:
  - Food Animal Microflora
  - Rhizosphere Effects
  - Aquatic Environment Effects
  - Occupational Hazards
  - Food Product Exposure

Food Animal Microflora

- Utilizing antibiotics prophylactically through fortified feed can select for antibiotic resistant bacteria in the microflora of food animals.
  - Food animals fed fortified feed were found to be 76 times more likely to have resistant enterococci species when compared to control groups.
  - In-feed tylosin increased the proportion of ery^R and tyl^R enterococci in the tylosin fed population, while the control group remained the same.
  - Multidrug resistance was also identified in enterococci isolates collected from food animals fed fortified feed.
- Antibiotics used in feed are also used for therapeutic purposes in food animals.
  - Lincomycin and tetracyclines, utilized to prevent disease in food animals, may eventually be ineffective with treating disease due to high levels of resistance correlated with overuse.

Food Animal Microflora Cont.

- Fortified feed was found to be ineffective with preventing disease, compared to earlier thoughts.
  - Tylosin, commonly used in feed at subtherapeutic doses for improving feed efficiency and to reduce liver abscesses, was found to have no effect with preventing abscesses as compared to subcutaneous injections.
- International positive correlations with antibiotic use and antibiotic resistance have been identified.
  - Belgium ranked first for 6 out of 7 antimicrobial classes utilized and showed the highest levels of antimicrobial resistance for most antimicrobial agents studied in any animal category.

Food Animal Microflora Cont.

- Removal of fortified feed can decrease antibiotic resistant microbes identified in the gastrointestinal tract of food animals.
  - After tylosin was removed from the study group, the proportion of ery^R and tyl^R resistant enterococci began to decrease until there was no significant difference between both treatment groups on day 225.

Rhizosphere Effects

- Utilizing antibiotic fed livestock manure as fertilizer in agriculture can negatively impact the rhizosphere, helping to perpetuate antibiotic resistance.
  - It is estimated that livestock excrete as much as 30-90% of veterinary antibiotics, which can be transferred to the soil via manure fertilization.
  - Tetracyclines were detected in the manure treatment fields at different depths and concentrations as compared to control fields.
  - A positive correlation between fields fertilized with manure from antibiotic fed livestock and the presence of both antibiotics and ARGs was identified; long-term manure applications increased antibiotic and ARG concentrations in the soil.
  - Long-term applications of sewage sludge and poultry manure soil fertilizer significantly increased the abundance and diversity of ARGs in soil environments.
  - ARGs and antimicrobial residues in manure can provide subtherapeutic pressures along with ARGs for horizontal gene transfer in soil, perpetuating antibiotic resistance.

Rhizosphere Effects Cont.

- Excreted ARGs found in soil can also impact crop production.
  - Plants grown in soil fertilized with antibiotic fed livestock manure were found to have ARGs in root endophytes, leaf endophytes and phyllosphere microorganisms.
  - Tetracycline resistant genes (tetA, tetAP and tetX) were detected in root endophytes and phyllosphere microorganisms.

Aquatic Environment Effects

- Excreted antimicrobials can alter the soil, which can be leeched into the aquatic environment via runoff.
  - Antimicrobials were detected in all water runoff samples from all livestock pens.
  - Antibiotics and ARGs were identified in both water and sediment samples from ditches, streams and rivers near manure treated fields.
  - Beta-lactamase resistance genes blaTEM and blaCTX-M9 along with penicillin resistance gene mecA were detected in all river samples due to animal fecal contamination. The more fecal contamination identified, the more resistance gene copies were present in the samples.

Aquatic Environment Cont.

- Antibiotics leeched into the waterways further impact environmental health by impacting the wastewater treatment plants (WWTPs).
  - Ofloxacin and ciprofloxacin had detection frequencies of 100% and 98% respectively across all WWTP sampling sites.
  - Fluoroquinolone concentrations in raw wastewater were as high as 1900 ng/L for ciprofloxacin and 600 ng/L for ofloxacin.
  - Antibiotic concentrations of 5µg/L were identified in WWTP samples, which is greater than normal concentrations less than 1µg/L. Antibiotic surface water concentrations that are less than 1µg/L do not impact WWTPs, while concentrations within 1-10µg/L can inhibit growth of specific microorganisms in biological processes of WWTPs or in down stream ecosystems, thus disrupting and contaminating these processes.
  - Antibiotic compounds that are not efficiently degraded may assist in maintaining or developing antibiotic resistant microbial populations.

Human Health: Occupational Hazards

- Overusing antibiotics in agriculture can have direct health effects on farm workers that have close working relationships with the food animals, leading to Livestock Associated MRSA (LA-MRSA) infections.
  - Of all the workers who tested positive for MRSA, 87% worked on farms where the sampled swine tested positive for MRSA.
  - 77% of workers who tested positive for MRSA were from farms with the highest prevalence of MRSA positive pigs.
  - A positive correlation existed between LA-MRSA and worker identified MRSA, the more prevalent MRSA infection was in the herd animals, the more prevalent it was in the farmers who worked with the animals, thus highlighting how shared environments can influence the health status of two species.
  - Furthermore, those individuals who spent more time on feeding calves, veterinary care, and stable management were more often MRSA carriers compared to those who spent less time with the livestock.

Human Health: Occupational Hazards Cont.

- Resistant infections in food animals can not only impact farmers, but also their family members, helping to spread disease further.
  - MRSA prevalence in calves, farmers, and family members was found to be 28%, 33% and 8% respectively.
  - Antibiotic usage was also associated with MRSA prevalence. Veal calves were often carriers when treated with antibiotics as compared to calves not treated. When less than 20% of the calves were MRSA carriers, the estimated prevalence in humans was approximately 1%. When MRSA prevalence increased in calves, the MRSA prevalence in humans was above 10%.
  - These findings denote how animal and human health can influence each other due to antibiotic usage and close proximity or increase in direct contact. Furthermore, these findings illustrate how these occupational risks can have far reaching health effects with family members testing positive for MRSA, thus negatively impacting community health.

Human Health: Food Product Exposure

- Contaminated animal products can also leave humans vulnerable to resistant bacterial infection via consumption, thus negatively impacting human health.
  - Samples collected from the hide, carcasses and meat products of food animals fed fortified feed and those that were not had similar antimicrobial-resistant *Escherichica coli* (AREC) prevalence, suggesting that antibiotic resistant bacteria, such as *E. coli* can be found on meat products after processing and pose a risk for human health through consumption.
  - Samples were also taken from the abattoir environment after processing both groups of cattle had AREC as well. Despite varying diets, both groups were found to have ARE in the meat products, which can enter the food chain regardless of whether or not cattle are administered AGP.
  - *Salmonella* and resistant *Salmonella* was also identified in 34% of chicken samples taken from a meat market in Anatolia, therefore, negatively impacting human health by causing resistant food borne infections that are challenging to treat.

Human Health: Food Product Exposure Cont.

- Livestock associated resistance genes were identified in human isolates.
  - Poultry-associated extended-spectrum β-lactamase (PA-ESBL) genes were identified in 35% of human isolates of *E. coli,* While 19% of those isolates contained PA-ESBL plasmids that were genetically indistinguishable from poultry meat samples.
  - Of the six ESBL genes identified in human samples, 86% were genes that were also predominant genes in both poultry (78%) and meat samples (75%).
  - These findings support the notion that ESBL genes and plasmids in humans occur through the food chain.
  - This route of infection could contribute to increased infections with ESBL producing bacteria in humans.

Human Health: Food Product Exposure Cont.

- The use of antimicrobials in food animals contributes to the occurrence of resistance in some bacterial species isolated from infections in humans.
  - Significant correlations were identified between resistance prevalence' to ampicillin, amiglycosides, third generation cephalosporins, fluoroquinolones for both human and poultry *E. coli* isolates.
  - Correlations were also identified with the amount of antimicrobials used and antimicrobial resistance towards fluoroquinolones and third generations cephalosporins.
  - Resistance in *E. coli* isolates from food animals, mainly poultry and pigs, correlated with resistance in isolates form people, supporting the hypothesis that many of the *E. coli* isolates that cause blood stream infections in people may be due to contaminated food sources.
  - Resistant *E. coli* could colonize the intestinal track of humans that can then cause subsequent infections from consuming contaminated food sources.

Discussion: Microflora

- This review identified strong correlations between food animals, environmental, and human health as a result of overusing antibiotics in agriculture for growth promotion purposes as well as disease prevention through fortified feed.
  - Fortified feed places subtherapeutic pressure on the microflora of food animals, thus selecting for resistant bacteria.
  - This can limit treatment options due to using the same antibiotics in fortified feed as are used to treat disease.
  - Fortified feed was also found to be an ineffective disease prevention measure, thus bringing into question the need for using fortified feed to prevent disease.
  - Removal of fortified feed looks promising as it can decrease the amount of resistant bacteria found in the fecal matter of food animals.

Discussion Cont.: Environment

- Altered microflora in food animals can produce trickle down effects that impact environmental health.
  - Excreted antibiotic residues and ARGs help to place subtherapeutic pressures on the soil and also provide genetic material for horizontal gene transfer.
  - This can contaminate produce grown in soil with ARGs or resistant bacteria. Human consumption of these products can lead to gastrointestinal illness.
  - Runoff from agricultural fields can further contaminate soil, streams and waterways in surrounding areas with antimicrobial residues and ARGs.
  - This can contaminate produce further via contaminated irrigated water.
  - Antibiotic residues and ARGs were also found in WWTPs, which can decrease the quality of drinking water and aquatic ecosystems by creating environments conducive for antibiotic resistance, thus impacting overall community health.

Discussion Cont.: Human Health

- Humans can also experience trickle down effects from fortified feed via occupational hazards and consumption of contaminated animal products.
  - Positive correlations were identified with the prevalence of antibiotic resistant microbes on livestock, farm workers, and family members, which highlights the relationship that exists between human and animal health.
  - Human and animal shared environments create opportunities for disease spread that can further impact community health.
- In order to prevent further impacts on animal, environmental, and human health, antibiotic overuse in agriculture needs to be addressed.

Discussion Cont.: Agricultural Changes

- Changes with agriculture feeding practices could be made that can improve overall health and decrease trickle down effects with antibiotic resistance.
  - Narrow grass hedges could be utilized to prevent or reduce the occurrence of agricultural runoff from areas receiving livestock manure.
  - The agricultural industry could reduce the amount of antimicrobials used in feed for both growth promotion purposes and disease prevention, thus gaining access to a wider global market.
    - Countries such as Denmark and Sweden have banned AGPs in feed and require veterinary prescriptions in order to use antibiotics in food animals.
    - This has resulted in a decrease in consumption and increase in production of weaning pigs from 18.4 million in 1992 to 27.1 million in 1998.
    - Sweden used AGPs to prevent necrotic enteritis in turkeys and the ban did not result in negative clinical effects or monetary losses for the farmers.
    - Changing current U.S. policy could expand our global market and improve the economy, while also improving overall community health. Further research into policy needs to be conducted in order to inform and direct U.S. policy change.

Discussion Cont.: Financial Implications

- Antibiotic misuse in agriculture can also create a financial burden for both humans and animals that acquire antibiotic resistance infections.
  - An animal could be euthanized if treatment costs outweigh treatment benefits, resulting in economic losses for farmers.
  - It is estimated that 2,049,422 illnesses and 23,000 deaths were caused by antibiotic resistance in humans.
    - *Clostridium difficile* infections can result in upwards of $1 billion in medical costs per year nation wide.
    - *ESBL* infections can cost $40,000 in excess hospital charges per occurrence.
    - This places financial strain on those individuals in need of care, thus highlighting the need for reform.

Conclusion

Human and animal health can impact one another, particularly in shared environments. Overusing antibiotics in agriculture can negatively impact animal health through microflora changes, which can cause trickle down effects with community and environmental health through excreted antibiotics and ARGs. Excreted antibiotics and ARGs can create selective pressures in the environment causing a decrease in both soil and water quality, which can impact crops and impact community health. Once antibiotic resistance is identified in both food animals and the environment, this puts humans at risk for contracting resistant bacteria through direct contact, consuming contaminated food products, and water sources. These findings and relationships exemplify how human, animal and environmental health are connected and influence one another through one unregulated facet. In order to adequately address this issue and produce lasting change, professionals from diverse backgrounds need to collaborate and seek change.

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