Policy Brief and Recommendations #5 Misuse of Antibiotics in Food Animal Production

Public Health Consequences of Antibiotic Use for Growth Promotion

POLICY BRIEF AND RECOMMENDATIONS #5
MISUSE OF ANTIBIOTICS IN FOOD ANIMAL PRODUCTION

DATE: SEPTEMBER 1, 2010
AUTHOR: APUA

PUBLIC HEALTH CONSEQUENCES OF ANTIBIOTIC USE FOR GROWTH PROMOTION

EXECUTIVE SUMMARY

Antibiotic growth promoters (AGPs) are particularly problematic from the resistance perspective, because they are used without veterinary prescription, administered for long periods of time at sub-therapeutic concentrations, and to entire groups or herds of animals. These conditions favor the selection and spread of antibiotic resistant bacteria among animals, to the environment and eventually to humans, where they cause infections that are more difficult to treat, longer lasting or more severe than antibiotic sensitive infections

AGP use in the United States should be terminated to protect public health. European data suggest that AGPs have little actual benefit in terms of growth promotion or increased feed efficiency. In some cases, however, they may have disease prophylaxis benefits. Therefore, AGP termination should be accompanied by appropriate steps to ensure that animal health and welfare is maintained in ways that do not result in significant increases in the use of therapeutic or prophylactic antibiotics that offset the benefits to public health from reduction in AGP use. This is possible though greater implementation of non-antibiotic strategies for animal health maintenance, and where necessary, more targeted use of therapeutic antimicrobials that are less likely than AGPs to select for resistance of public health importance.

INTRODUCTION

Antibiotics are widely used for growth promotion in food animal production in the United States. Some of the antibiotics used for growth promotion in pigs, poultry and/or cattle are classified by the World Health Organization (WHO) as critically important antibiotics for use in human medicine [1]. Antibiotic growth promoters (AGP) are particularly problematic for resistance, because they are used without veterinary prescription and are administered for long periods of time at sub-therapeutic concentrations to entire groups or herds of animals.

These conditions favor the selection and spread of antibiotic resistant bacteria among animals, to the environment and eventually to humans, where they cause infections that are more difficult to treat, last longer or are more severe than antibiotic sensitive infections [2].

Options to address the resistance problems of AGP use include doing nothing, restricting use to those that do not select for antibiotic resistance of importance to human or veterinary medicine, or to stop using them altogether in food animal production [3]. The United States has essentially followed the first option. European countries initially adopted the second option, but in recent years banned the use of all AGPs in food animal production [4]. The purpose of this brief is to describe the public health consequences of using AGP in food animals and options for reducing these consequences

Public health consequences of growth promoter use

Recent research implicates food animals as an important reservoir for urinary tract and blood stream infections in people

Food animals are an important reservoir of non-typhoidal *Salmonella*, as well as *Campylobacter* and some types of *E. coli* infections of humans [5], [6], [7], [8]. Recent research suggests that food animals (particularly pigs) may also be a reservoir of some strains of methicillin resistant *Staphylococcus aureus* (MRSA) for humans, although it appears that people are the major reservoir for most epidemiologically important strains of MRSA [9]. While the major public health impact from food animals is normally attributed to foodborne *Salmonella* and *Campylobacter*, recent research is making it increasingly apparent that food animals are also an important reservoir of antibiotic resistant *E. coli* urinary tract and probably bloodstream infections of humans ([8], [10].

AGPs used in the United States include members of important classes of antibiotics used in humans, including penicillins (B-lactams), macrolides, tetracyclines, streptogrammins, sulfonamides and others. Fortuitously, avoparcin, a member of the glycopeptide class that includes vancomycin, was never approved for AGP or therapeutic use in the United States as it was in Europe and elsewhere. This was not because of resistance concerns, but because of evidence that residues of the drug in edible tissues from treated animals would be toxic to humans [11]. As a consequence of decades of widespread use in the United States, resistance to the AGPs is very common in pathogenic and commensal bacteria from food animals.

For example, the prevalence of resistance to tetracyclines, sulfonamides and beta lactams among fecal *E. coli* from pigs and poultry is typically greater than 20%, and in some cases greater than 90% [12], [13]. Importantly, AGPs also exert selective pressure to other antimicrobials of great importance to human medicine through the process of co-selection [5], [3]. These resistant bacteria may colonize or cause infections in people exposed through contaminated food, by direct contact with infected animals, or indirectly through contaminated water or other environmental sources. Importantly, some of these bacteria that acquire resistance determinants in animals (e.g. *Enterococcus faecium*, *E. coli*) may colonize humans and share these genes with other human pathogens. In some cases, these altered pathogens may spread to other people in hospitals or other settings, in the face of additional antibiotic selection pressures in people [5], [2].

Antibiotic resistance increases the human burden of illness

Antibiotic resistance among enteric pathogens of humans increases the burden of illness in humans by increasing the total number of infections that occur (through altered colonization resistance), and increasing the severity and duration of infection [2], [14]. The precise burden of illness attributable to AGP use and antimicrobial resistance selection is unknown, due to lack of comprehensive epidemiological studies and risk assessments that account for the tremendous complexity of the farm animal / environment / human ecosystem. Various risk assessments of limited scope have been conducted to estimate the magnitude of public health impact of antimicrobial use in animals on certain types of antibiotic resistance. The results vary from minimal impact in the case of certain macrolides and selection of resistance in enterococci [15] to many thousands of additional cases of fluoroquinolone resistant *Campylobacter* infections annually in the United States [16].

Antibiotic use in food animals select for antibiotic resistant infections in humans

Research in the United States and Europe has shown that the risk of death and hospitalization is greater in resistant than sensitive *Salmonella* infections [17], [18],[19]. Many studies have shown that people taking antibiotics are at increased risk of acquiring antibiotic resistant infections [20], [21]. Since person-to-person spread of non-typhoidal Salmonella is rare in the United States, resistance to these *Salmonella* is most likely to have been selected by antibiotic use in animals.

Options for containment of resistance – agriculture

It is well recognized that resistance is a problem in food animal production, but there is a lack of consensus on what to do about it. The main options available to improve antibiotic use on farms are to maintain the *status quo* (i.e. do nothing), ban or restrict the use of specific antibiotics, limit their use to specific situations or conditions through altered licensing, attempt to modify behavior in order to improve "prudent use" practices among veterinarians and farmers, remove incentives to excessive use, and reduce the need for antibiotics by improving vaccines, non-antibiotic growth enhancers, and improved hygiene and health management on farms [3].

Doing nothing is not a viable option, because resistance continues to increase and is an unacceptable public health burden. Banning or otherwise withdrawing the use of antibiotics in specific situations has been successful in reducing antibiotic use and resistance. For example, the ban on use of avoparcin and other AGPs in Denmark resulted in the dramatic decline in glycopeptides use and resistance among enterococci (Figure 1) [4]. In Canada, the voluntary (but temporary) withdrawal of use of ceftiofur for injection of hatching eggs or day-old chicks dramatically reduced resistance to 3rd generation cephalosporins in *Salmonella* from humans and chickens [22]. Unfortunately, the industry has at least partially resumed ceftiofur use, and resistance has increased accordingly (figure 2).

Most antibiotics licensed without prior consideration of resistance risks to humans

Improved licensing has potential for reducing resistance impacts, particularly for new classes of antibiotics that are not yet approved for use in animals. Unfortunately, most of the antibiotics now on the market were licensed without prior consideration of antibiotic resistance risks to humans. Once on the market, it has proven to be extremely difficult to remove those that pose risks to human health. For example, several years ago FDA proposed to revoke the approvals for penicillin and tetracycline as growth promoters, but was unsuccessful [23]. Moreover, once approved for use in at least one type of food animals, veterinarians have considerable latitude in prescribing extra-label use in other food animal species.

There are many advocates for the voluntary "prudent use" approach to antibiotic stewardship, which involves adherence to general principles of antibiotic use that maximize therapeutic efficacy but minimize resistance risks [5]. Unfortunately, there is little evidence that this approach has actually changed prescribing or use behavior in the veterinary sector, or has had any impact on antibiotic use or resistance in food animal production. Furthermore, there is no real incentive for veterinarians or farmers to improve their antibiotic use practices, since they receive no financial benefit from producing animals shedding fewer resistant human pathogens or commensals. If anything, there are important financial incentives that drive increased use in food animals.

Alternatives for decreasing use of antibiotics in agriculture

Since antibiotics are generally effective in preventing and treating clinical bacterial infections of animals (the vast majority of which are not human pathogens), farmers realize fewer losses through morbidity and mortality, when antibiotics are used for these purposes. Another incentive to increased use is the financial remuneration received by some veterinarians, who supply antibiotics to farmers. While antibiotics for humans in the United States are normally dispensed through pharmacies and hospitals, veterinarians frequently both prescribe and dispense these drugs and in some cases, may realize considerable profit from doing so. In some European countries, veterinarians are no longer allowed to profit from antibiotic sales, and there is good evidence that this reduces antibiotic use on farms [4].

There are many alternatives to antibiotics. Many of these (e.g. vaccines, health management programs) are already used on good quality farms and probably reduce the need for antibiotic use. Unfortunately, some veterinarians and farmers seem willing to rely on antibiotics to treat bacterial infections rather than prevent them in the first place, or to use antibiotics as cheap and effective options for prophylaxis of bacterial infections. Widespread introduction of health management practices can improve animal health, and, therefore, the need for treatment or prophylaxis. For example, introduction and routine use of a vaccine for farmed salmon in Norway dramatically reduced the quantity of antibiotics used in production (figure 3) [24], [25]. There can be little doubt that the continued ready access to cheap in-feed antibiotics is an important disincentive to development and widespread uptake of additional vaccines and other alternatives to antibiotics.

Terminate use of antibiotics for growth promotion

U.S. public policy on the misuse of antibiotics in agriculture is severely lagging. *AGP use in the United States should be terminated* [26], [5]. This widespread use of antibiotics at low doses for long periods of time selects for resistance to antibiotics of importance to human medicine [26]. Such resistance increases the frequency, severity and duration of important human infections, such as *Salmonella*, *Campylobacter* and *E. coli*. European data suggest that benefits to animal production from AGP use are limited or negligible. To the extent that AGPs are preventing some bacterial infections of animals, termination may have some adverse effects. Most of these effects can be anticipated, and may include increased incidence of necrotic enteritis in poultry and diarrhea in piglets. *Suitable alternatives that can be put in place, include vaccines and where necessary, more targeted use of antibiotics that do not select for resistance to critically important antibiotics for humans* [26]. *Steps will have to be taken, however, to ensure that veterinarians and farmers do not simply compensate for decreased AGP use by directly increasing use of prophylactic antimicrobials. Quantitative data on antimicrobial use in agriculture should be made available to make assessments to inform animal and public health policy [26]*[*].

This policy brief is made possible with the support of The Pew Charitable Trusts.

References

1. Collignon, P., et al., *World Health Organization ranking of antimicrobials according to their importance in human medicine: A critical step for developing risk management strategies for the use of antimicrobials in food production animals.* Clin Infect Dis, 2009. **49**(1): p. 132-41.
2. Barza, M., *Potential mechanisms of increased disease in humans from antimicrobial resistance in food animals.* Clin Infect Dis, 2002. **34 Suppl 3**: p. S123-5.
3. Aarestrup, F.M., H.C. Wegener, and P. Collignon, *Resistance in bacteria of the food chain: epidemiology and control strategies.* Expert Rev Anti Infect Ther, 2008. **6**(5): p. 733-50.
4. World Health Organization. Dept. of Communicable Disease Prevention Control and Eradication., Danish Veterinary Institute., and Danmarks jordbrugsforskning, *Impacts of antimicrobial growth promoter termination in Denmark : the WHO international review panel' s evaluation of the termination of the use of antimicrobial growth promoters in Denmark : Foulum, Denmark 6-9 November 2002*. 2003, Geneva: World Health Organization. 57 p.
5. World Health Organization. Division of Emerging and other Communicable Diseases Surveillance and Control., *The Medical impact of the use of antimicrobials in food animals : report of a WHO meeting, Berlin, Germany, 13-17 October 1997*. 1997, Geneva: World Health Organization. 24 p.
6. National Academy of Sciences. *The use of drugs in food animals, benefits and risks.* in *Committee on Drug Use in Food Animals*
1999. Washington, D.C.: National Academy Press.
7. FAO/WHO/OIE. in *Joint FAO/WHO/OIE Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific Assessment.* 2003. Geneva, Switzerland.
8. Collignon, P., *Resistant Escherichia coli--we are what we eat.* Clin Infect Dis, 2009. **49**(2): p. 202-4.
9. Weese, J.S. and E. van Duijkeren, *Methicillin-resistant Staphylococcus aureus and Staphylococcus pseudintermedius in veterinary medicine.* Vet Microbiol, 2010. **140**(3-4): p. 418-29.
10. Manges, A.R., et al., *Retail meat consumption and the acquisition of antimicrobial resistant Escherichia coli causing urinary tract infections: a case-control study.* Foodborne Pathog Dis, 2007. **4**(4): p. 419-31.
11. McDonald, L.C., et al., *Vancomycin-resistant enterococci outside the health-care setting: prevalence, sources, and public health implications.* Emerg Infect Dis, 1997. **3**(3): p. 311-7.

[*] For more information and detailed policy recommendations, see the FAAIR Report edited by Michael Barza, MD and Sherwood L. Gorbach, MD.

12. Alali, W.Q., et al., *Longitudinal study of antimicrobial resistance among Escherichia coli isolates from integrated multisite cohorts of humans and swine.* Appl Environ Microbiol, 2008. **74**(12): p. 3672-81.
13. Smith, J.L., et al., *Impact of antimicrobial usage on antimicrobial resistance in commensal Escherichia coli strains colonizing broiler chickens.* Appl Environ Microbiol, 2007. **73**(5): p. 1404-14.
14. Heuer, O.E., et al., *Human health consequences of use of antimicrobial agents in aquaculture.* Clin Infect Dis, 2009. **49**(8): p. 1248-53.
15. Hurd, H.S., et al., *Public health consequences of macrolide use in food animals: a deterministic risk assessment.* J Food Prot, 2004. **67**(5): p. 980-92.
16. Nelson, J.M., et al., *Fluoroquinolone-resistant Campylobacter species and the withdrawal of fluoroquinolones from use in poultry: a public health success story.* Clin Infect Dis, 2007. **44**(7): p. 977-80.
17. Holmberg, S.D., J.G. Wells, and M.L. Cohen, *Animal-to-man transmission of antimicrobial-resistant Salmonella: investigations of U.S. outbreaks, 1971-1983.* Science, 1984. **225**(4664): p. 833-5.
18. Varma, J.K., et al., *Hospitalization and antimicrobial resistance in Salmonella outbreaks, 1984-2002.* Emerg Infect Dis, 2005. **11**(6): p. 943-6.
19. Helms, M., J. Simonsen, and K. Molbak, *Quinolone resistance is associated with increased risk of invasive illness or death during infection with Salmonella serotype Typhimurium.* J Infect Dis, 2004. **190**(9): p. 1652-4.
20. Glynn, M.K., et al., *Prior antimicrobial agent use increases the risk of sporadic infections with multidrug-resistant Salmonella enterica serotype Typhimurium: a FoodNet case-control study, 1996-1997.* Clin Infect Dis, 2004. **38 Suppl 3**: p. S227-36.
21. Koningstein, M., et al., *The interaction between prior antimicrobial drug exposure and resistance in human Salmonella infections.* J Antimicrob Chemother, 2010. **65**(8): p. 1819-25.
22. Dutil, L., et al., *Ceftiofur resistance in Salmonella enterica serovar Heidelberg from chicken meat and humans, Canada.* Emerg Infect Dis, 2010. **16**(1): p. 48-54.
23. Institute of Medicine. *Human health risks with the subtherapeutic use of penicillin or tetracyclines in animal feed.* 1989. Washington, D.C.: National Academy Press.
24. Sorum, H., *Farming of Atlantic salmon--an experience from Norway.* Acta Vet Scand Suppl, 2000. **93**: p. 129-34, discussion 149-57.
25. FAO/WHO/OIE. in *Expert Consultation on Antimicrobial Use in Aquaculture and Antimicrobial Resistance.* 2006.
26. FAAIR, *Policy recommendations.* Clin Infect Dis, 2002. **34 Suppl 3**: p. S76-7.

Figure 1: (see title below – from reference 6)

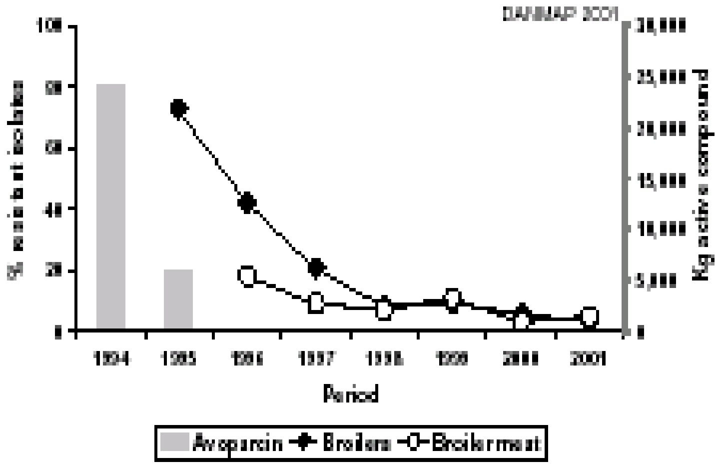

Figure 11. Trend in avoparcin resistance among Enterococcus faecium *from broilers and broiler meat and the usage of the growth promoter avoparcin, Denmark*

Figure 2: Proportion (moving average of previous three quarters) of isolates resistant to ceftiofur among retail chicken E. coli, and retail chicken and human clinical *S.* Heidelberg isolates from 2003 to 2008 (preliminary) in Québec and Ontario.* (Reprinted from reference below)

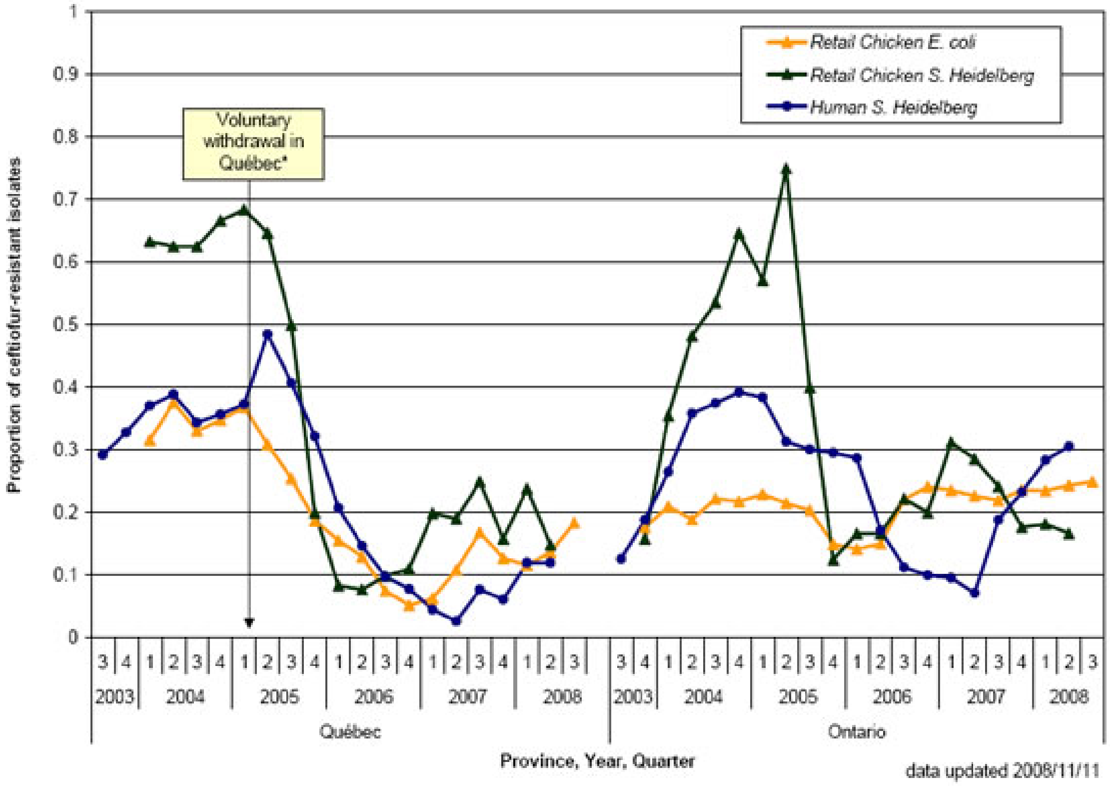

Figure 3: Antimicrobial Usage in relation to Production of Salmon and Trout Production in Norway (from Report FAO/OIE/WHO Expert Consultation on Antimicrobial Use in Aquaculture and Antimicrobial Resistance, 2006)