Informing Public Policy on Agricultural Use of Antimicrobials in the United States: Strategies Developed by an NGO

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The Alliance for the Prudent Use of Antibiotics (APUA) instituted its Facts about Antimicrobials in Animals and the Impact on Resistance (FAAIR) project in 1999. The purpose of FAAIR is to review and analyze scientific data on the subject of antimicrobial use in agriculture in order to inform public policy. The specific objectives of FAAIR include: 1) increasing public understanding of the ecological and public health issues surrounding antimicrobial use in agriculture, 2) fostering communication among stakeholders concerning its benefits and risks, and 3) influencing policy makers to implement measures for improved use.

In order to meet these goals, APUA convened a Scientific Advisory Panel of nationally recognized clinicians and researchers with relevant areas of expertise. The Panel includes epidemiologists, microbiologists, physicians, a statistician, and a veterinarian. Four of the Panel members have also been members of the committee that produced the 1988 report *Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed* for the Institute of Medicine (1).

Panel members met at the APUA Headquarters in Boston on twelve occasions to develop a comprehensive report, *The Need to Reduce Antimicrobial Use in Agriculture: Ecological and Human Health Consequences* (The FAAIR Report). In addition to the fifty-plus hours spent deliberating as a group, Panel members have devoted many hours to researching and writing their individual chapters. The Report also reflects the concerns expressed by a group of stakeholders at a series of meetings convened by APUA, as well as comments made by four outside reviewers from government and industry. APUA is extremely grateful to the Panel members as well as the stakeholders and reviewers for their valuable contributions to the Report.

The FAAIR Report begins with two chapters discussing the extent of antimicrobial use in food animal and plant agriculture (Chapters 1-2). Most food animals in the United States are exposed to antimicrobials in feed, water or by injection at some point in their lives. These medications are used to treat or prevent infectious disease, to promote growth, and/or increase feed efficiency. Few reliable data describing the extent and quantity of antimicrobial use in animals are publicly available in the U.S. In plant agriculture, most antibiotic use is prophylactic, as antibiotics tend to be ineffective once disease is already present. Antibiotic use in plant agriculture is a particular area of concern because spraying (the most common application method) tends to promote entry of antibiotics into the environment, particularly the water supply.

The next two chapters of the FAAIR Report (Chapters 3-4) address the origin and spread of resistance genes and the persistence of antimicrobial resistance. These chapters explain that antimicrobials exert intense selective pressure for resistance, which acts on rare genes that are already present in the population or random mutations. Once resistance emerges, it can spread rapidly through various genetic mechanisms, even between commensal and pathogenic bacteria. When antibiotic use stops, the selective pressure is removed, and resistant bacteria can become diluted by susceptible ones. However, resistance can sometimes persist, especially when resistance genes are linked to other genes or through "plasmid addition systems."

Chapter 5 reviews the epidemiological evidence for a linkage between the use of antibiotics in food animals and infections due to resistant strains of foodborne pathogens in humans. Such evidence can be direct, through molecular analysis, or indirect, through temporal sequencing of antibiotic use and the emergence of resistance. Examples of direct evidence include a study that shows a clear chain of evidence between the illicit use of chloramphenicol in farm animals to chloramphenicol-resistant *S. newport* infection in humans (2). Examples of indirect evidence include studies of fluoroquinolone resistance in *Campylobacter* in poultry and humans after the addition of fluoroquinolones to animal feed (3, 4), vancomycin-resistant enterococci after the use of avoparcin in poultry (5, 6, 7), and the emergence of resistance in vancomycin-resistant enterococci to streptogramin antibiotics used in poultry (8).

The final chapters of the FAAIR Report (Chapters 6-9) deal with risk assessment and evidence that the agricultural use of antibiotics imposes a burden on human health. Chapter 6 reviews the strengths and weaknesses of existing risk assessment models relating foodborne infections in humans to the use of antibiotics in food animals. Chapter 7 proposes five possible mechanisms by which antimicrobial resistance could have a negative impact on human health. Proposed mechanisms include: 1) additional infections in people taking antimicrobials for other reasons, 2) additional virulence genetically linked to resistance, 3) delays in treatment due to undetected resistance, 4) increased total pathogen load due to antibiotics, and 5) reservoirs of resistance in commensal bacteria.

Chapter 8 examines the first mechanism in detail, attempting to calculate the "attributable fraction" or excess number of *Salmonella* and *Campylobacter* infections in patients taking antimicrobials for other reasons. This increase in human disease due to resistance is thought to occur because antimicrobials facilitate colonization by eliminating susceptible commensal bacteria. Finally, Chapter 9 elaborates on the second and third mechanisms, reviewing evidence on increased virulence and delays in treatment due to initial choice of an antibiotic to which the pathogen is resistant.

To summarize, the FAAIR Report begins by presenting evidence on the extent of antibiotic use in agriculture. It then addresses the means by which resistance elements can spread among bacterial populations and the epidemiological evidence for transfer of pathogens between food animals and humans. Finally, it addresses issues of risk assessment and mechanisms by which agricultural use of antibiotics can impact human health.

One of the most important themes of the Report is an ecological perspective on the issue of antimicrobial resistance. The use of antimicrobials in food animals creates a selective pressure for the emergence of antimicrobial resistance in bacteria of these animals. Because these resistance bacteria can be transmitted to humans through the food supply or by contact with the animals or their environment, these resistance determinants contribute to an environmental pool of resistance.

While all use of antimicrobials contributes to the global pool of resistance, certain categories of agricultural use may be especially problematic because of the size of the treated populations, the duration of treatment, and the dosage administered. This is one

reason that reliable data on the quantities of antimicrobials produced and used in the US for agriculture are necessary for the formulation of appropriate policy. This need will be addressed in the second phase of the FAAIR project, which will be completed in 2003.

In addition to the need for more reliable estimates of antibiotic usage, the FAAIR Panel also identified the need for more coordinated and comprehensive antibiotic resistance surveillance efforts directed at both human food-borne illnesses and animal infections. These data will substantively inform future models of the human health risk associated with antibiotic usage in farm animals. The Panel also noted that current risk assessment models do not, in general, account for indirect ecological risks to human health associated with agricultural antibiotic usage. Such risks may include the emergence of antibiotic resistance genes linked to those selected for by the use of a particular antibiotic or environmental persistence of antibiotics used in agriculture. Surveillance efforts should be expanded to investigate such possibilities, and the data produced should be incorporated into future risk assessment models.

The FAAIR Report culminates in a series of Conclusions and Policy Recommendations intended to improve public policy on the agricultural use of antimicrobials in the United States. In the Policy Recommendations, the Panel suggests practical strategies to encourage more appropriate use of antimicrobials in agriculture.

The FAAIR Report will be published in its complete form as a supplement to the journal *Clinical Infectious Diseases.* It will also be accessible to non-subscribers on the publication's website. In order to make the information and analysis contained in the Report as accessible as possible, APUA is also preparing a summary document, targeted at a non-scientific audience. This document will be distributed to policy makers, stakeholders, and the media. Through the FAAIR Report, APUA intends to convince scientists, government officials, and the general public of the need to reduce unnecessary antimicrobial use in agriculture in order to preserve the effectiveness of these drugs for future generations.

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