ANTIBIOTIC FEED ADDITIVES: POLITICS AND SCIENCE*

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SUMMARY

The debate regarding the use of antibiotic feed additives in food-producing animals has intensified in recent years fueled by activist groups opposed to conventional animal agriculture that use this issue, as well as those of food safety, animal welfare and environmental pollution to further their cause, scare the public and ultimately impose their views on society. In the author's opinion, the goal of some of the most extreme activist groups is to convert the entire society to vegetarianism. The media in general and some politicians have seized the opportunity to gain higher ratings and more votes by sensationalized reporting and legislative proposals to restrict their use in the USA (HR-962; S-549). In spite of more than 50 years of use and an endless search for a "smoking gun", to the author's knowledge, to this date, not a single human fatality has been linked directly and unequivocally to the use of antibiotic feed additives in food animal production. Contrary to public perception, the continued use of antibiotic feed additives is beneficial for both, animal and human health. As detailed in this article, there are numerous scientifically documented benefits derived directly from their use such as the prevention and control of enteric diseases, enhanced food safety, improved animal welfare, preservation and less contamination of the environment, improved efficiency of production and lower cost of production resulting in lower prices for the consumers who can continue to enjoy an abundant supply of safe and nutritious food products of animal origin at an affordable price.

INTRODUCTION

The debate about whether antibiotics should be added to animal feeds at low or subtherapeutic levels dates back to the beginning of their use as feed additives in food-producing animals. Since the Swann report was made public in 1969, the common practice of adding antibiotics at low levels to the feed of animals destined for human consumption has been further scrutinized for its potential to create antibiotic resistance (M.M. Swann, 1969). The Swann report suggested that antibiotic feed additives from the same classes used in human medicine not be used in food-producing animals. More recently, the World Health Organization has also made similar suggestions but has been willing to allow continued usage when proper scientific risk assessments have been conducted (WHO, 2000). Numerous scientific reviews have been conducted to determine if this practice poses a significant risk to human health. Most scientific reviews (NRC, 1998; Bezoen, et. al., 1999; USGAO, 1999; I. Phillips, et. al, 2004; IFT Expert Report, 2006) acknowledge the fact that feeding low levels of antibiotics to food-producing animals can result in the development of antibiotic resistant bacteria and therefore a theoretical risk to humans that come in contact with the animals or consume their products, as they have acknowledged the theoretical risk to humans posed by house pets

that have been treated with antibiotics. Likewise, the scientific reviews have concluded that antibiotic use in humans is the driving force behind the antibiotic resistance problems encountered in human medicine and that the practice of feeding low levels of antibiotics to food-producing animals poses no immediate or imminent threat to human health, as this practice has been in existence for over 50 years and to this date there has not been a single documented human fatality unequivocally linked to their use in food-producing animals.

THE ARGUMENT USED AGAINST ANTIBIOTICS

The activist groups opposed to the routine use of antibiotics at low or subtherapeutic levels in poultry feeds frequently state that poultry companies unnecessarily feed millions of pounds of antibiotics each year to promote growth and enhance feed efficiency in otherwise "healthy flocks" of broiler chickens and turkeys. They also claim that poultry companies use antibiotic feed additives as crutches to continue raising poultry flocks in filthy and poorly managed conditions. What these groups fail to recognize is that nearly one half of the total amount of antibiotics added each year to poultry feeds belong to a class of antibiotic feed additives known as polyether ionophores that are primarily used for the purpose of preventing coccidiosis in broiler and turkey flocks, and have no use in human medicine (AHI, 20005). Even the most risk averse European Union (EU) regulators recognize this fact and have not banned the use of antibiotics of the polyether ionophore class for coccidiosis prevention in food-producing animals.

The activist groups have also failed to recognize that the beneficial effects of antibiotic feed additives on poultry health and welfare have been scientifically documented in "healthy chickens" maintained under ideal conditions of sanitation and management (E. Roura, et. al., 1992). Researchers from the University of California demonstrated that indicators of immunologic stress, such as elevated plasma levels of interleukin-1, elevated serum levels of copper and elevated liver concentrations of metallothionein, could be induced in broiler chicks exposed to a dirty environment or given an injection of *Salmonella typhimurium* lipopolysacharide. In addition, the chicks with signs of immunologic stress also had lighter body weights and higher feed conversions than the chicks without signs of immunologic stress. In all experiments, the chicks that were fed low levels of antibiotics in the feed had significantly lower levels of indicators of immunologic stress, heavier body weights and lower feed conversions. Interestingly, "healthy chicks" kept in clean environments under optimal management conditions also showed signs of immunologic stress, and the addition of low levels of antibiotics to their feed significantly lowered them resulting in heavier body weights and lower feed conversions leading the researchers to conclude that, "We were able to reduce signs of an immune response taking place in 'healthy' growing chicks housed according to conventional laboratory guidelines by feeding antibiotics, suggesting that activation of the immune system sufficient to impair growth occurs across a wide range of conditions of sanitation".

Finally, the activist groups fail to recognize that poultry companies strive to raise poultry flocks under the best possible management practices as healthy flocks perform better and are more profitable.

THEORY *VS.* REALITY

The basis for the opposition to the use of antibiotics at low levels in animal feeds for food-producing animals comes from concerns about the development of antibiotic resistance in bacteria present in the animals and the potential for the transfer of those antibiotic-resistant bacteria to the public through the food chain. Although at first glance this may seem like a reasonable concern, a more in-depth examination of the data currently available on antibiotic-resistant bacteria of significance in human medicine leads to a different conclusion.

For example, of the 20 most serious bacterial infections exhibiting problems with antibiotic resistance in human medicine, 12 are in no possible way related to antibiotic use in food-producing animals as these bacteria cannot be acquired via the food chain. Of the remaining 8, assuming that transfer of bacterial resistance from animals to people occurs (an unproven assumption in most cases), the calculated percent contribution to antibiotic resistance in all cases is 1% or less, and in most cases is less than 0.5% (Bywater and Casewell, 2000). Likewise, results from the SENTRY Antimicrobial Surveillance Program, which since 1997 has analyzed worldwide data on antibiotic resistance patterns from both, human and animal bacterial isolates has found little significant association between human and animal patterns (Jones and Turndige, 2003). According to Ron Jones, MD, results from the SENTRY Antimicrobial Surveillance Program "clearly show a disconnect between antibiotic resistance patterns in humans and animals, calling into question the alleged link between resistant bacteria in animals and those in humans". These conclusions are further supported by data collected in the USA by the National Antibiotic Resistance Monitoring System (NARMS), which includes antibiotic resistance data from indicator bacteria collected from humans by the Centers for Disease Control and Prevention (CDC) and animals by the U.S. Department of Agriculture (NARMS, 2004).

THE POLITICS:
EUROPEAN UNION SEQUENCE OF EVENTS

Sweden was the first country to unilaterally ban the routine use of all antibiotics added to animal feeds in low levels in 1986. At that time Sweden was not a member of the EU. The Swedish model was then supported by other Scandinavian countries like, Denmark and Finland. When Sweden and Finland entered the EU in 1995, special derogations from EU laws were permitted so that they could continue their ban of in-feed antibiotics (P.E.V. Williams, 2001). However, as the extended derogations from EU laws were to expire at the end of 1998 and were contrary to the policy of the EU which allowed the use of in-feed antibiotics in the rest of the member countries, the Scandinavian countries put additional lobbying efforts to persuade the EU Commission to enact the same policy in regards to the use of in-feed antibiotics throughout the remaining EU member countries.

As political pressure from the Scandinavian countries mounted to affect a change in EU policy with regards to the use of in-feed antibiotics, an independent analysis was conducted by the University of Gent in Belgium to determine the feasibility of applying the Swedish model to the rest of the EU (Viaene, 1997). The conclusions from this

analysis were not favorable as it pointed out the significant loss in production efficiency and increased costs associated with the ban of antibiotic feed additives. The analysis also pointed out the high economic cost associated with the Swedish ban of in-feed antibiotics manifested by increased use of feed, lowered production efficiency and higher use of antibiotics for therapeutic purposes while not detecting a measurable improvement in antibiotic resistance in people. In the same report it was indicated that the ban had created an adverse impact of animal production on the environment by increasing the demand for animal feeds and water, and the production of animal waste products. It was also stated that the use of alternative methods used in food-producing animals in an attempt to prevent enteric diseases, like the use of zinc oxide as a feed additive, had resulted in the contamination of the land with increased concentrations of zinc, a heavy metal. The report also indicated that the EU was facing increased competition in export markets and concluded that with open world markets the European producers should have access to all the tools available to improve production efficiency, including the antibiotic feed additives. It is important to keep in mind that all the antibiotic feed additives classed as "growth promoters" that were being questioned by Sweden had already past a stringent EU regulatory review in regards to their efficacy and safety for animals, people and the environment.

Since there was disagreement between the Swedish and the Belgian analyses of the Swedish model, the EU Commission asked the Scientific Committee on Animal Nutrition (SCAN) to review all the available information and make a recommendation. The SCAN was established in 1976 as an advisory scientific committee to the EU Commission in matters pertaining to the use of feed additives in food-producing animals. The SCAN is composed of a group of expert scientists from various EU member countries appointed to the committee for their recognized scientific excellence.

THE E.U. BANS ON ANTIBIOTIC FEED ADDITIVES:
AVOPARCIN

The first antibiotic feed additive to undergo review by the SCAN was avoparcin, and although the expert scientists of the SCAN did not recommend its ban (SCAN, 1996); the EU Commission banned its use anyway as an antibiotic feed additive for food-producing animals in 1997. Concerns about the potential spread of vancomycin-resistant enterococci (VRE) from food-producing animals to people through the food chain were cited as the reason for the ban and the precautionary principle was invoked to implement the ban. Avoparcin belongs to the glycopeptide class of antibiotics, and so does vancomycin, an antibiotic considered critically important in human medicine. Although VRE will develop in food-producing animals fed avoparcin and the same VRE have been detected in raw meat of animals fed avoparcin as a feed additive, the preponderance of evidence suggests that its transmission to people does not occur to the degree that could impact human health adversely. For example, the prevalence of VRE infections in people in the EU before the ban was much lower than in the USA, in spite of the fact that avoparcin had been fed extensively for many years to food-producing animals in the EU. In contrast, the prevalence of VRE infections in hospitalized patients in the USA is much greater than in the EU, in spite of the fact that avoparcin has never been fed to food-producing animals in the USA (I. Phillips, 1999; J. Acar, et. al., 2000; I. Phillips, 2004; IFT Expert

Report, 2006). The only conclusion that can be reached is that vancomycin use in humans, rather than avoparcin use in food-producing animals, is responsible for the development of VRE infections of significance in human health.

VIRGINIAMYCIN

The second antibiotic feed additive to undergo review by the SCAN was virginiamycin, like in the case of avoparcin, the SCAN did not recommend its ban (SCAN, 1998). Nevertheless, the same rationale applied to the avoparcin ban was used by the EU Commission to justify the ban of virginiamycin in 1999, invoking the precautionary principle and citing concerns about the potential spread of streptogramin-resistant *Enterococcus faecium* (SREF) from food-producing animals to people through the food chain. In addition to virginiamycin, the EU Commission banned also the use of bacitracin, tylosin and spiramycin as antibiotic feed additives for food-producing animals (European Commission, 1998). Quinupristin-dalfopristin (Q-D) is an antibiotic used to treat hospital-acquired infections in humans caused by vancomycin-resistant *Enterococcus faecium* (VREF). Q-D belongs to the streptogramin class of antibiotics, and so does virginiamycin. Although SREF will develop in food-producing animals fed virginiamycin and the same SREF have been detected in raw meat of animals fed virginiamycin as a feed additive, the preponderance of evidence suggests that its transmission to people does not occur to the degree that could impact human health adversely (I. Phillips, 1999; J. Acar, et. al., 2000; L.C. McDonald, et. al., 2001; A.L. Kieke, et. al., 2006). A very extensive sensitivity survey conducted in American and Canadian medical clinics before Q-D use began in North America found that out of more than 1,000 clinical isolates of *E. faecium* tested, 99.8% were sensitive to the new human antibiotic (R.N. Jones, et. al., 1998). Therefore, this study showed that after nearly 3 decades of continuous use of virginiamycin in food-producing animals in the USA and Canada, there was virtually no evidence of SREF in the human population. These results are not surprising since meat is cooked prior to its consumption, and the high temperatures achieved during cooking kill any bacteria that might have contaminated it, and dead bacteria cannot transmit antibiotic resistance. The importance of proper food hygiene and cooking has been pointed out by others as the most effective way of preventing not only transmission of antibiotic-resistance bacteria but also of preventing food poisoning in people (I. Phillips, et. al., 2004). More recently, this opinion has been seconded by a panel of internationally renowned experts in the field of antibiotic resistance that concluded that, "applying interventions to control foodborne pathogens in general, rather than focusing on antibiotic-resistant strains specifically, would have the greatest impact in reducing overall foodborne illnesses" (IFT Expert Report, 2006). Evidence is also mounting that confirms that *E. faecium* have host specificity that prevents *E. faecium* of chicken origin to colonize people and vice versa (R.J.L. Williems, et. al., 2000), and that enterococci responsible for hospital-acquired infections are genetically different to all the ones isolated from food-producing animals (R.J.L. Williems, et. al., 2001).

A study published in The New England Journal of Medicine which was specifically designed to prove the transfer of SREF from chickens to people, failed to do so (L.C. McDonald, et. al., 2001). Between July 1998 and June 1999, the researchers cultured 407

raw chickens obtained from 26 grocery stores in 4 states, and isolated SREF from 58.2% of them. Resistance was defined as a minimum inhibitory concentration (MIC) of at least 4 ppm. The authors attributed the high level of resistance to the use of virginiamycin. During the same period the authors also cultured 334 stool samples from outpatients at various medical clinics in the same 4 states. In contrast to the significant level of resistance found in the raw chickens, only 2 stool samples, or 0.6% of the total yielded SREF. It is worth noting that both samples had an MIC of 4 ppm reported by the authors as a "low level" resistance. In spite of these results, the authors concluded that, "although the low prevalence and low level of resistance in human stool specimens suggest that the use of virginiamycin in animals has not yet had a substantial influence", and that, "foodborne dissemination of resistance may increase", and finally that, "the Food and Drug Administration (FDA) was in the process of conducting a risk assessment for virginiamycin and that if such assessment demonstrated a role for foodborne transmission in the emergence of SREF in humans, restrictions on the continued use of virginiamycin in food animals should be considered".

These results agree with the findings of a more recent study also specifically designed to show the transfer of SREF from chickens to people and interpreted by the authors as casting doubt on the use of virginiamycin in food-producing animals (A.L. Kieke, et. al., 2006). This study compared the prevalence of SREF between 567 hospital patients, 100 healthy vegetarians, 160 retail samples from conventionally grown chickens and 26 retail samples from antibiotic-free grown chickens. *Enterococcus faecium* were isolated from 105 patients (105/567 = 18.5%), 65 vegetarians (65/100 = 65%), 77 conventional (77/160 = 48.1%) and 23 (23/26 = 88.5%) antibiotic-free retail samples. As in the study previously discussed, the researchers found no SREF in any of the human samples whereas they found SREF in 56% of the retail samples from conventionally-grown chickens, indicating no detected transmission of SREF from chickens to people. Moreover, *E. faecium* were isolated from a significantly higher proportion of vegetarians than of self-reported chicken eaters (65 vs. 18.5%) and from a significantly higher proportion of antibiotic-free grown chickens than conventionally grown chickens (88.5 vs. 48.1%). Not satisfied with the results, the researchers resorted to quantifying what they called the "inducible resistance" of the *E. faecium* isolates from all groups by first growing the isolates in a conventional medium and then transferring a sample during the log phase of growth to a BHI broth that already contained 0.25 mcg/ml of virginiamycin where the cultures were allowed to grow for 24 hours. After that period, the bacterial density was readjusted in a fresh BHI broth that already contained 8 mcg/ml of quinupristin-dalfopristin (Q-D) where the cultures were allowed to grow for an additional 24 hours. The level of inducible Q-D resistance was expressed as relative growth, by comparing the optical density of the culture pre-exposed to virginiamycin and subsequently challenged with Q-D with that of the same culture without virginiamycin pre-exposure before the challenge with Q-D. Through this series of steps, the authors constructed an outcome measure that, in their judgment, suggested higher "inducible resistance" among isolates from conventionally-grown chickens. Even the authors of the study recognized and acknowledged some serious caveats in the design and interpretation of their study. For example, comparing hospital patients to healthy vegetarians is not a valid comparison, nor does it represent the largest segment of the population (healthy

meat eaters). That crucial group was noticeably omitted. The researchers also acknowledged that, "Although the multivariable analysis adjusted for many factors, confounding may have occurred, and other factors associated with vegetarian status may have contributed to the observed associations". More fundamentally, the study used statistical associations for a highly contrived index of inducible resistance to reach a conclusion that implicated chicken as a possible resistance risk, even though the data clearly showed that there was no SREF in any human patient and that the risk of having *E. faecium* isolated was smaller among chicken eaters than healthy vegetarians, and also smaller among conventionally grown chickens than antibiotic-free grown chickens.

THE SCIENCE:
VIRGINIAMYCIN RISK ASSESSMENTS

Two risk analyses have been conducted for virginiamycin. A quantitative risk analysis showed that the risk of the continued use of virginiamycin as an antibiotic feed additive in food-producing animals, assuming that transmission of resistance from foods derived from animals to people occurs (an unproven assumption in this case), is negligible and rapidly decreasing by the increased use of newer antibiotics as alternatives to Q-D (Cox and Popken, 2004). The Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) also completed its own risk assessment and also concluded that the risk from the continued use of virginiamycin in food-producing animals is very small (USFDA-CVM, 2004). The FDA risk assessment concludes that with a food pathway attribution assumption of 10% the average risk to a random hospitalized member of the US population, the most relevant "at risk" population, of having SREF attributable to animal uses of virginiamycin and that may result in impaired Q-D therapy, ranges from 6 chances in 100 million to 1.2 chances in 1 million in one year, and that with a food pathway attribution assumption of 100% the chances would increase 10-fold. To present a comparative perspective on risk, the following example is provided from an article on risk assessment of fluoroquinolone use in beef cattle (S.A. Anderson, et. al., 2001). A study had estimated approximately a 1-in-250 million chance that a person could die from a case of *Campylobacter jejuni* infection that is resistant to fluoroquinolone antibiotics, which the person might have acquired by eating contaminated ground beef. In comparison to this risk, in any given year a person is 567 times more likely to be killed in a plane crash and 14,284 times more likely to be killed in a car crash.

Since regulators always tend to focus on the risk of continuing a practice and seldom examine the risk of discontinuing that same practice, an additional quantitative risk analysis examined both, the risk and benefit, derived from the continued use of virginiamycin as an antibiotic feed additive in food-producing animals (L.A. Cox, Jr., 2005). The analysis was based on a new quantitative technique known as Rapid Risk Rating Technique (RRRT) that estimates and multiplies exposure based on existent data, dose-response and consequence factors as suggested by the WHO to estimate the impacts on human health from withdrawing virginiamycin (WHO, 2003). The increased human health risks associated with a ban of virginiamycin from more pathogens reaching consumers were predicted to far outweigh the benefits from reduced streptogramin-resistant vancomycin-resistant *Enterococcus faecium* (SRVREF) infections in human

patients. More specifically, an estimated increase of 6,660 cases of campylobacteriosis per year *vs.* an estimated increase of 0.27 cases of SRVREF per year.

Due to all of this and the thorough examination of many other published research reports, a panel of experts concluded that, "there is little or no evidence that resistant enterococci from animals are a risk to human health", and that "a ban of growth promoting antibiotics was not justified on this basis, and will have no impact on the prevalence of VRE in human infections" (I. Phillips, et. al., 2004). Similar conclusions have been reached by other scientific reviews like the HAN report from the Netherlands that concluded that, "Documented *in-vivo* cases showing spread of antimicrobial resistant Gram positive bacteria from livestock to humans are in essence non-existent" and that, "the continued use of antibiotic feed additives presents no imminent hazard to public health" (A. Bezoen, et. al., 1999).

MORE POLITICS:
THE FINAL BANS

The use for growth promotion in food-producing animals of the remaining antibiotic feed additives (avilamycin, bambermycin, monensin and salinomycin) was banned in the EU effective January 1, 2006. This ban included products that have no analogues used in human medicine but the EU Commission, once more, invoked the precautionary principle to justify the ban.

THE E.U.'S DOUBLE STANDARD

A double standard exists in regard to antibiotic use in food-producing animals in the EU, as poultry, swine and cattle are in most cases not raised "antibiotic-free" but rather raised without antibiotic growth promoters. As mentioned before, the lack of prophylactic use of antibiotic feed additives has resulted in higher prevalence of enteric disease outbreaks in food-producing animals, which in turn has resulted in more frequent use of antibiotics for treatment of sick animals, unfortunately the antibiotics used for treatment are from those classes that are much more commonly prescribed in human medicine than the ones used in the feed before the bans. As pointed out by various groups of experts (M. Casewell, et. al., 2003; I. Phillips, et. al., 2004; IFT Expert Report, 2006), and as evidenced from the continuous yearly increases in the amount of antibiotics prescribed for food-producing animals in Denmark, from 48,000 kilograms the year after the bans to 112,650 kilograms in 2005 (DANMAP, 1996-2005), it is becoming increasingly clear, that the use of the growth promoters was accompanied by other, previously unrecognized, health promotional and prophylactic benefits.

THE FOCUS ON FOOD-PRODUCING ANIMALS

From the results previously discussed, it is clear that even if one assumes that antibiotic resistance transfer from animals to people occurs (an unproven assumption in most cases), the potential contribution of food-producing animals to the overall antibiotic resistance problem would be minimal to nil (Bywater and Casewell, 2000). On the other hand, a two-year survey on antibiotic resistance in a community, conducted by researchers from Wales and published in the British Medical Journal (J.T. Magee, et. al., 1999) clearly documents the positive correlation between antibiotic prescribing practices

in a community and the development of antibiotic resistance in the people from the same community. The number of prescriptions written on a yearly basis per 1000 patients produced practically a mirror image when compared to the average resistance rate in bacteria isolated from surgical samples from the community hospital. In all cases, the higher the number of prescriptions written for a given antibiotic, the higher the average resistance rate in the bacteria tested from the surgical samples.

Therefore, it is distressing to see that for the most part the antibiotic resistance debate has remained restricted to antibiotic use in food-producing animals. Clearly, from all the scientific reviews of the subject and even with the acknowledgement of the WHO, antibiotic prescription by medical doctors in human practice is the driving force behind the antibiotic resistance problem. Also clearly, of the 2 distinct animal populations, food-producing animals and companion animals, and as pointed out by others (D.A. Barber, 2001; S. Simjee, 2002; H. Cervantes, 2003, 2004; D.A. Barber, et. al., 2003), companion animals are a much more likely source of antibiotic resistance transfer to humans than food-producing animals.

Dogs, cats and other companion animals get treated with the same classes of antibiotics commonly prescribed in human medicine with little to no supervision by any regulatory agency, in much the same way as those prescribed by medical doctors, and on any given period, humans and companion animals consume on average 10 times more antibiotics per unit of body weight than food-producing animals (D. Barber, 2001). In addition, companion animals often share living quarters with their owners increasing the likelihood of bacterial transfer, so it is difficult to comprehend why scientists, regulators and politicians are most concerned with antibiotic use in food-producing animals, instead of antibiotic prescribing practices by medical doctors and companion animal veterinarians.

One has to wonder if there are other factors, such as the fear of taking on the American Medical Association or the American Veterinary Medical Association, or on the known emotional bond between people and their pets, that are causing the debate to remain primarily restricted to antibiotic use in food-producing animals.

THE CONSEQUENCES FROM THE E.U. BANS:
ANIMAL HEALTH AND PRODUCTIVITY

A report by researchers from the National Veterinary Institute of Oslo, Norway (Lovland and Kaldhusdal, 2001) documented severely impaired production performance in broiler flocks with high incidence of *Clostridium perfringens*-associated hepatitis (CPAH). The authors analyzed production performance data collected from a large processing plant in Norway, with the objective of comparing production performance data from broiler flocks with high levels of CPAH to flocks with low levels of CPAH. The study was conducted for two and a half years following the ban of avoparcin, the first antibiotic feed additive banned by the EU. This study showed that flocks with high levels of CPAH had 25 to 43% lower profitability than those with low levels. The authors cited impaired feed conversion and reduced weight at slaughter as the major causes for the losses. Researchers from the same Institute had reported earlier that the main effects of experimentally-induced subclinical necrotic enteritis were precisely increased feed

conversion and retarded growth rate (Kaldhusdal and Hofshagen, 1992). So it has become increasingly evident following the EU bans that the antibiotic feed additives, like avoparcin and virginiamycin, were preventing clinical and subclinical necrotic enteritis in poultry, even when used at inclusion rates labeled for "growth promotion", this is in agreement with the observations made by others (I. Phillips, et. al., 2004; H. Cervantes, 2005; IFT Expert Report, 2006; Bafundo and Cervantes, 2006).

In another report, the authors examined data 3 years after the bans were implemented and concluded that the only measurable benefit in humans was a reduction in acquired resistance in enterococci isolated from human fecal carriers, however, the authors stated that despite the growth promoter ban and the reduction of carriage of resistant enterococci in animals and humans, there had been no reduction in the prevalence of resistant enterococcal infections in humans (M. Casewell, et. al., 2003). On the other hand, the authors also stated that the antibiotic feed additives had an important prophylactic activity previously unrecognized and that their withdrawal was now associated with a deterioration in animal health, evidenced by an increased incidence of diarrhea, weight loss and mortality in post-weaning pigs, and necrotic enteritis in broiler chickens. The authors closed by saying that "the theoretical and political benefit of the widespread ban of growth promoters needs to be more carefully weighed against the increasingly apparent adverse consequences".

RESULTS OF BANS ON HUMAN HEALTH

An unintended consequence of the EU ban on the prophylactic use of antibiotic feed additives in food-producing animals may have an even greater adverse effect on public health. Researchers reported that following the EU bans, the incidence of *Clostridium perfringens*-associated disease in poultry and its detection in poultry meat has increased substantially and its emerging as a real threat to public health (F.V. Immerseel, et. al., 2004.) According to the report, with the ban of the remaining 3 antibiotic feed additives (avilamycin, monensin and salinomycin) with activity against *C. perfringens*, the public threat of *C. perfringens*-induced food poisoning is expected to increase even more. Time will tell the magnitude of the consequences of the bans on antibiotic feed additives on human health.

Likewise, a more recently published report by a panel of internationally renowned experts in the field of antibiotic resistance (IFT Expert Report, 2006) concluded that, "there is evidence that there are significant human health benefits from subtherapeutic antibiotic use to prevent subclinical disease in food animals and reduce levels of *Salmonella* and *Campylobacter* contamination of poultry carcasses".

According to the latest available report by DANMAP (2005), "the use of antibiotics in humans and animals and the occurrence of resistant bacteria continued to increase through 2005". In the mean time, antibiotic use for therapeutic purposes in food-producing animals has increased every year since the first bans, from 48,000 kilograms the year after the bans to 112,650 kilograms in 2005. The report further details that the consumption of beta-lactamase sensitive penicillins, penicillin-streptomycin combinations, macrolides and tetracyclines has continued to increase. Likewise,

antibiotic consumption in cattle (including dairy) increased by 5% while there was no change in antibiotic consumption in poultry. At the same time the report indicated that there was a sharp increase of 5.1% in antibiotic consumption in humans. According to the report the reasons for the steady increase in consumption of antibiotics in humans have yet to be determined. Likewise, antibiotic consumption in Danish hospitals continued to increase, on average by 48%. Paralleling these increases in consumption, further increases in the prevalence of bacterial isolates resistant to cephalosporins and fluoroquinolones were reported. Therefore, it has become increasingly clear that the ban on antibiotic feed additives has not translated into less therapeutic antibiotic use in food-producing animals or less antibiotic resistance in humans. This is in agreement with the conclusions of other experts (Bedford and Fothergill, 2003; R.J. Bywater, 2005; I. Phillips, 2007).

A professor of veterinary medicine has recently proposed an interesting theory on how antibiotic feed additive usage in food-producing animals may actually reduce the risk of food poisoning in consumers (H.S. Hurd, 2005). His hypothesis seems to be in agreement with a published manuscript that indicated, for example, that the use of virginiamycin in turkey feeds significantly reduced the incidence of *Salmonella spp*. (N. Cox, et. al., 2003), since virginiamycin has no direct activity on *Salmonella spp*., it must be assumed that the changes produced in the intestinal microflora were less favorable to its growth. Likewise, the use of antibiotics, whether added to the feed to prevent disease or in the drinking water to treat diseases like airsacculitis of poultry, may also aid in reducing the risk of food poisoning to consumers. In a series of studies conducted to determine the effect of airsacculitis of broiler chickens on the overall quality of the carcass (S.M. Russell, 2003), the researcher found that airsacculitis-positive flocks had lower body weights, more fecal contamination, more processing errors and higher levels of *Campylobacter spp*. The author concluded that broiler chicken companies should emphasize control of airsacculititis in flocks as a means of preventing subsequent foodborne bacterial infection. Unfortunately, FDA has recently banned the use of enrofloxacin in poultry, the most effective drug to treat airsacculitis. This ban was carried out in spite of FDA continuing to allow the use of enrofloxacin in beef cattle in the USA and the EU continuing to allow the use of enrofloxacin in poultry.

It has also been reported that concentrations of various antibiotic feed additives and ionophore anticoccidials similar to those normally used in poultry rations had an inhibitory effect on the transfer of a multiresistance-conferring plasmid in *E. coli* in an *in-vitro* test system (J.J. Mathers, et. al., 2004). The authors concluded that based on the results of these test, feed additive antibiotics and ionophore anticoccidials may actually inhibit resistance transfer mechanisms within poultry and livestock.

These observations appear to have been confirmed by a series of recently reported quantitative risk assessments aimed at determining the risk and benefits to human health from the continued use of antimicrobials in food-producing animals, in which several surprising conclusions were reached (L.A. Cox, Jr., et. al., 2007). One was that the use of antimicrobials that benefit animal health may also benefit human health. Another one was that the antibiotic bans carried out by the EU had the unintentional consequence of

increased illness rates in humans (and hence increased antimicrobial use and resistance rates). Their new models based on quantitative risk assessments provide a better tool to government regulators and industry stakeholders to make better decisions for the benefit of human and animal health.

MORE SCIENCE:
THE BENEFITS FROM USING ANTIBIOTICS

Frequently overlooked on this debate are the substantial benefits derived from the use of antibiotic feed additives in food-producing animals. The benefits are significant and of importance for both, animal and human health.

Listed below are scientifically documented benefits from the inclusion of low levels of antibiotics in animal feeds:

Prevention of subclinical diseases, such as necrotic enteritis in poultry. This is the main reason antibiotic feed additives are used at subtherapeutic levels in animal feeds, because they are used to prevent subclinical disease. Subclinical necrotic enteritis of poultry has been shown to have a significant adverse impact on flock performance and condemnations at the processing plant (Khaldhusdal and Hofshagen, 1992; Lovland and Khaldhusal, 2001). Previous research has demonstrated that the effectiveness of an antibiotic feed additive to improve performance parameters such as growth rate and feed conversion is directly correlated with its ability to control *Clostridium perfringens*, the causative agent of clinical and subclinical necrotic enteritis of chickens and turkeys (Stutz and Lawton, 1984). All but one of the antibiotic feed additives used in poultry production in the USA and classed as "growth promoters" have a FDA-approved claim for the prevention or control of necrotic enteritis (Feed Additive Compendium, 2007).

Reduction of human pathogens, by improving flock uniformity, enhancing intestinal strength, minimizing gastrointestinal ruptures during evisceration and processing, and by reducing shedding of human pathogens such as *Salmonella spp*. and *Campylobacter spp*. the use of antibiotic feed additives in animal feeds ultimately enhances the safety of the final product for the consumer (S.M. Russell, 2003; N.A. Cox et. al., 2003; H.S. Hurd, 2005). Chickens raised for the organic market without antibiotics have been shown to have a prevalence of *Campylobacter spp*. almost three times greater than that of conventionally-grown chickens (O.E. Heuer, et. al., 2001).

Improved animal welfare, because antibiotic feed additives have been scientifically shown to reduce immunologic stress even in "healthy chickens" kept under optimal sanitary, environmental and management conditions, their use contributes to enhance the welfare of food-producing animals (E. Roura, et. al., 1992).

Improved production efficiency, this benefit is the result of better enteric health and prevention of nutrient degradation by the intestinal microflora. Typically, growth rate and feed conversion are improved which has led to class these additives as "growth promoters", given what we have learned since this old term was coined many years ago, and the consequences from banning their use in the EU (M. Casewell, et. al., 2003; I.

Phillips, et. al., 2004, IFT Expert Report, 2006; I. Phillips, 2007), where the prevalence of enteric diseases and the use of therapeutic antibiotics in food-producing animals have increased significantly since the bans, a more appropriate name would have been "health promoters" (H. Cervantes, 2006a,b,c,d,e).

Preservation and less contamination of the environment, due to the improvements attained in growth rate and feed conversion, the same meat output can be maintained with a reduced number of animals and farms, and a reduced number of tons of feed resulting in more acres of the environment being preserved in its natural state. A recent scientific presentation estimated that a 0.04 improvement in feed conversion attributed to the use of antibiotic feed additives in a commercial turkey production operation would eliminate the need for an additional 5,525 tons of feed that without them would have had to have been produced and delivered, and as a consequence, an additional amount of excreta corresponding to this increase in feed tonnage would have been produced and disposed of into the environment without any additional gain in meat production (Tilley and Gonder, 2007). Assuming that turkeys drink two units of water for each unit of feed, an additional 11,050 tons of water would have also been used up with the increase in feed tonnage taking more natural resources from the environment without any additional benefit.

Lower prices for the consumer, since with the use of antibiotic feed additives production efficiency is improved, the savings from the cost of production can be passed on to the consumers who can continue to enjoy an abundant supply of nutritious and safe meats at an affordable price. This is the main reason the use of antibiotic feed additives in third world countries has not decreased and is not likely to decrease in the foreseeable future.

ARE THERE ANY VIABLE ALTERNATIVES?

As of this writing, and as acknowledged by others (Bedford and Fothergill, 2003; Dibner and Richards, 2005; T.A. Niewold, 2007), there are no alternatives to the antibiotic feed additives in food-producing animals. Numerous compounds have been tried but none have the ability to combat or prevent bacterial infections, reduce immunologic stress and the inflammatory response like the antibiotics can. In an effort to explain why the highly reproducible effects seen with the antibiotic feed additives cannot be reproduced with other alternatives aimed at modifying the microflora of the gastrointestinal tract, Niewold (2007) hypothesized that the real mode of action of the antibiotic feed additives is not primarily due to their antibacterial action at the gastrointestinal level but rather to their suppressing effect on the production and excretion of catabolic mediators produced by intestinal inflammatory cells. His hypothesis agrees with the findings reported earlier by other researchers that showed that feeding low levels of antibiotics to "healthy" broiler chicks had a positive effect on indicators of immunologic stress and the inflammatory reaction (Roura et. al., 1992). Initially, it was generally accepted that the effect of the antibiotic feed additives was entirely due to their antibacterial action at the intestinal level since their use in germ-free chicks did not result in significantly improved performance parameters like growth rate and feed efficiency (M.E. Coates, et. al., 1963).

CONCLUSIONS

There are numerous scientifically documented benefits such as the prevention of subclinical diseases, reduction of human pathogens, improved animal welfare, enhanced production efficiency, preservation and less contamination of the environment, lower costs of production and lower meat prices for the consumer that are directly derived from the inclusion of antibiotic feed additives at low levels in animal feeds (E. Roura, et. al., 1992; I. Phillips, et. al., 2004; IFT Expert Report, 2006).

Antibiotic feed additives have been included at low or subtherapeutic levels in feeds consumed by animals destined for human consumption for over 50 years. In spite of an endless search for a "smoking gun", to the best of the author's knowledge, not a single human fatality caused by antibiotic treatment failure can be conclusively and unequivocally linked to the use of antibiotic feed additives in animal feeds. Numerous scientific reviews on the subject have acknowledged the fact that antibiotic-resistant bacteria can develop in animals fed low levels of antibiotics, and that those bacteria may reach the public through the food chain posing a theoretical risk to human health (M.M. Swann, 1969; NRC, 1998; A. Bezoen, et. al., 1999; USGAO, 1999). However, there is little to no evidence to support the claim that the use of antibiotic feed additives in animals feeds has contributed to the problem of antibiotic resistance in human medicine since their use has been in existence for many years without any measurable adverse effects on human health (I. Phillips, 1999; I. Phillips, et. al., 2004; IFT Expert Report, 2006). The scientific reviews also acknowledge the fact that antibiotic use by humans is the driving force behind the antibiotic resistance problems encountered in human medicine, as they have also acknowledged the fact that house pets treated with antibiotics may pose an even greater risk of transfer of antibiotic-resistant bacteria to people due to the intimate association between people and their pets.

The EU Commission banned the use of all antibiotic feed additives classed as growth promoters in the EU against the advice of its own Scientific Committee on Animal Nutrition (SCAN, 1996; SCAN, 1998). Certain Scandinavian countries that had already unilaterally banned the use of some or all antibiotics at low levels in animal feeds put political pressure on the EU Commission to impose their policy across all EU member countries (P.E.V. Williams, 2001). The Commission succumbed to the political pressures from the Scandinavian countries and banned the use of all antibiotic feed additives classed as growth promoters starting with avoparcin in 1997 and ending with the remaining antibiotic feed additives on January 1, 2006. Since all the antibiotic feed additives had passed stringent regulatory reviews for efficacy and safety for animals, humans and the environment, the EU Commission had to resort to the precautionary principle to implement the ban.

Almost immediately after the ban a surge of enteric disease problems in food-producing animals arouse. The surge in enteric diseases of food-producing animals was followed by a surge in antibiotic use in food-producing animals for therapeutic purposes. The antibiotics used to treat food-producing animals belong to the same classes of antibiotics most frequently used in human medicine, this might have actually had a more adverse effect on the creation of antibiotic resistance in people than the use of the antibiotic feed additives (H. Cervantes, 2006d,e; I. Phillips, 2007). The surge in use of antibiotics for

therapeutic purposes in food-producing animals has clearly proven that the prior use of antibiotic feed additives had a health promotional and disease prevention effect in food-producing animals even when used at concentrations labeled for “growth promotion”.

Although the antibiotic feed additive bans implemented by the EU achieved the objective of reducing the prevalence of resistance in indicator bacteria in raw food products of animal origin, this has not resulted in any measurable improvement on the problem related to antibiotic resistance in human patients or human hospitals (M. Casewell, et. al., 2003; Bedford and Fothergill, 2003; K. Bafundo, 2004; I. Phillips, et. al., 2004; IFT Expert Report, 2006; I. Phillips, 2007). Data from the Danish database known as DANMAP on human and veterinary consumption of antibiotics and antibiotic-resistant bacteria have shown a continued increase in the amount of antibiotics prescribed for therapeutic purposes in food-producing animals every year since the first ban of avoparcin. Along with this increase there has been an increased rate of illnesses and consumption of antibiotics in both, food-producing animals and humans while simultaneously there has been an increase in the detection of antibiotic resistant bacteria in both, food-producing animals and humans in most EU member countries. This is in agreement with the most recent reviews that have concluded that along with the increased use of therapeutic antibiotics in food-producing animals, there has also been an increased rate of illnesses and antibiotic usage in people from the EU, with almost universal increases in the prevalence of antibiotic-resistant bacteria. Clearly, the ban of antibiotic growth promoters enacted by the EU did not achieve the ultimate desired effect as therapeutic antibiotic usage and antibiotic-resistant bacteria have continued to increase in humans (I. Phillips, 2007).

While the prevalence of foodborne diseases in the USA population has continued to decline, its prevalence in the EU has continued to increase, at least for certain bacteria like *Salmonella*, *Campylobacter* and *C. perfringens*. Therefore, it is becoming increasingly clear that the bans on antibiotic feed additives have not resulted in a safer food supply.

Antibiotic-resistance is an extremely complex problem that is not fully understood and does not lend itself to simplistic solutions like the banning of the antibiotic feed additives. Research continues to produce surprising findings, for example, University of Georgia researchers recently reported that chicks raised under pristine laboratory conditions and never exposed to antibiotics had a significant prevalence of antibiotic-resistant bacteria (J.L. Smith, et. al., 2007).

As it has been learned from the EU experience, it is not only important to assess the risk of continuing a practice (like the feeding of subtherapeutic levels of antibiotics to food-producing animals) but it is equally or even more important to assess the risk of discontinuing that same practice. As it has been learned from the EU experience, discontinuing a practice for political reasons without the proper risk analysis may have results opposite to its intended ones.

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