

ASSESSING THE RESULTS OF THE EUROPEAN UNION BAN ON ANTIBIOTIC FEED ADDITIVES

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INTRODUCTION

The European Union (EU) banned the use of avoparcin, a widely used antibiotic feed additive in food-producing animals in 1997. The ban was carried out against the advice of the Scientific Committee on Animal Nutrition (21), a panel of experts composed of animal scientists from various EU countries. Two years later, the EU banned the use of bacitracin, spiramycin, tylosin and virginiamycin, once more the ban was carried out against the expert scientific advice of the SCAN (1, 22), citing fears of antibiotic resistance spread via the food chain and invoking the precautionary principle.

On January 1, 2006 the remaining antibiotic feed additives used in food-producing animals will be banned from use in the EU (13). Because several years have passed since the EU bans on antibiotic feed additives were implemented, and because some politicians in the USA are proposing a similar ban in this country (11, 24), it would seem appropriate to conduct an assessment of the ban results to determine if such bans have had a measurable effect on the problem of antibiotic resistance in human medicine. The purpose of this manuscript will be to evaluate and discuss published scientific information in regards to the EU bans on antibiotic feed additives and conclude if they have had a positive, a negative or no effect on the health of food-producing animals and on the problem of antibiotic resistance in human medicine.

BAN RESULTS ON ANTIBIOTIC RESISTANCE

Most likely the oldest and most complete source of data regarding antibiotic use and antibiotic resistance monitoring in animals and people is the Danish database known as DANMAP, therefore, data from these reports will be used to illustrate the results and conclusions reached in this manuscript.

As anticipated, the antibiotic feed additive bans have resulted in substantially lower levels of antibiotic resistance for the corresponding antibiotic on indicator bacteria isolated from raw meat products. This should not surprise anyone, since it is a known fact that with a few exceptions, antibiotic use will create antibiotic resistance, whether in animals or people. What the DANMAP data shows, however, is that the improvements seen on indicator bacteria isolated from raw meats have not translated into lower levels of antibiotic resistance in human patients (10, 5, 9, 20). There is an abundant body of published scientific information that serves to explain this lack of correlation.

The first antibiotic feed additive used in food-producing animals banned in 1997 by the EU was avoparcin. This antibiotic was banned from use in food-producing animals because it belongs to the glycopeptide class, a critically important antibiotic used in human medicine, vancomycin, also belongs to this class and studies have shown that glycopeptide-resistant enterococci will develop in animals fed avoparcin (8), also resistant enterococci have been isolated from raw meat of animals fed avoparcin creating a concern for passage of resistant enterococci to people via the food chain (6). This is what led to the ban of avoparcin as an antibiotic feed additive in the EU.

However, when one examines the incidence of vancomycin-resistant enterococci (VRE, bacteria commonly involved in fatal infections in human hospitals), a different picture emerges. That is because VRE infections are far more prevalent in USA hospitals than in EU hospitals (1, 19), and since avoparcin has never been used as an antibiotic feed additive in food-producing animals in the USA, it must be concluded that 100% of the VRE problem has been created by vancomycin use in humans. Obviously, a ban on antibiotic feed additives in the USA would do nothing to improve the critical VRE problem in USA hospitals. Although studies in Europe have shown that VRE can be isolated from healthy human and animal feces, the relatively low prevalence of VRE in hospitalized EU patients suggests that without substantial use of vancomycin in human medicine, the VRE problem would be very limited (19,20).

Another antibiotic feed additive used in food-producing animals banned by the EU in 1999 is virginiamycin. This antibiotic belongs to the streptogramin class and as in the case of avoparcin, concerns over cross-resistance with a new human antibiotic in the same class, Synercid, developed for treatment of vancomycin-resistant *E. faecium* (VREF) infections prompted EU regulators to call for its ban as an antibiotic feed additive in food-producing animals.

However, a very extensive sensitivity survey conducted in American and Canadian medical clinics before Synercid 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 (14). 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 streptogramin-resistant *E. faecium* (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 (20).

Another study published in 2001 in The New England Journal of Medicine (18) which was specifically designed to prove the transfer of SREF from foods of animal origin to people, failed to do so. Between July 1998 and June 1999, the authors 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”, “foodborne dissemination of resistance may increase”, they concluded by saying 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 food borne transmission in the emergence of SREF in humans, restrictions on the continued use of virginiamycin in food animals should be considered”.

Since that manuscript was published, two risk analysis have been conducted. 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 animal foods to people occurs (an unproven assumption in this case), the risk would be less than one statistical life saved for the entire USA population over a 15 year period and rapidly decreasing by the increased use of newer antibiotics as alternatives to Synercid (7). FDA 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. 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 Synercid 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 (2), 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 caught 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.

It is because of all of this and the thorough examination of many other published research reports, that 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” (20).

BAN RESULTS ON ANIMAL HEALTH AND PRODUCTIVITY

A manuscript by researchers from the National Veterinary Institute of Oslo, Norway (16) reported in 2001 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 the first 2.5 years following the ban of avoparcin, the first antibiotic feed additive to be 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 increased feed conversion and retarded growth rate (15). So it has become increasingly clear 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 (20).

In another manuscript (5), 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 infection in humans. 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”.

BAN RESULTS 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. In a manuscript published in December, 2004 (13) the authors indicate that following the EU bans, the incidence of *C. perfringens*-associated disease in poultry and its detection in poultry meat has increased substantially and it is emerging as a real threat to public health. According to the authors, toxins formed by *C. perfringens* type A and type C present in poultry meat can cause food poisoning and necrotic enteritis in people, respectively. Since *C. perfringens* food poisoning is not a reportable disease, its incidence is in all probability greatly underestimated. Nevertheless, *C. perfringens* was recognized in Norway as the most common cause of food poisoning during the decade of the 1990s (3). According to F.V. Immersel, et.al., 2004, 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 as related to food poisoning in humans.

According to the latest available report by DANMAP, “the use of antibiotics in humans and animals and the occurrence of resistant bacteria continued to increase through 2004”. 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 112,500 kilograms in 2004.

An interesting theory has recently been proposed on how antibiotic use in food-producing animals may actually reduce consumer risk (12), a professor of veterinary medicine provided various ways by which antibiotic feed additive use in food-producing animals may actually lower the risk of food poisoning in people. This seems to be in agreement with a recently published manuscript that indicated for example, that the use of virginiamycin in turkey feeds significantly reduced the incidence of *salmonella spp.* (7), since virginiamycin has no direct activity on *salmonella spp.*, we must assume 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 (an infection of the air sacs) of broiler chickens on the overall quality of the carcass (23), 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 airsacculitis in the flocks as a means of preventing subsequent food borne bacterial infection.

Finally, it has recently 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 (17). The authors concluded that based on the results of these tests, feed additive antibiotics and ionophore anticoccidials may actually inhibit resistance transfer mechanisms within poultry and livestock.

CONCLUSIONS

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. This conclusion is further supported by the fact that 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, in most cases less than 0.5% (4).

The EU banned the use of various antibiotic feed additives at levels labeled for growth promotion. Almost immediately a surge of enteric disease problems in food-producing animals followed. 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 various 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. 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 incidence of resistance on 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. This may be explained by the fact that monitoring of antibiotic resistance in raw meat products is not representative of the bacteria that may actually reach the consumer. Proper cooking of foods of animal origin destroys any bacteria that might have contaminated them, and dead bacteria cannot transmit antibiotic resistance to people.

While the incidence of food borne diseases in the USA population has continued to decline, in the EU it has continued to increase, at least for certain bacteria like salmonella, campylobacter and *C. perfringens*. Therefore, it is becoming increasingly apparent that the bans on antibiotic feed additives have not resulted in a safer food supply.

The USA should learn from the EU experience and proceed with caution and only make decisions supported by science and quantitative risk analysis rather than implementing bans that may actually have effects opposite to their intended ones.

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