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ANTIBIOTIC RESISTANCE IN THE EU – SCIENCE, POLITICS, AND POLICY

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A number of resistant bacterial pathogens have become the focus of recent concern in human medicine. Studies and facts on use of antibiotics in animals suggest that animal sources contribute little to the problem. The current pursuit of zero risk by banning some antibiotics in Europe is not a sensible precaution but rather an abdication of responsibility based on science.

Key words: animals; antibiotics; Europe; health policy; precaution; resistance.

By definition, bacteria are selected for resistance when exposed to an antibiotic. This natural biological process, which results in the survival of the most resistant strains, was observed long before the discovery of penicillin. Some bacteria are also already naturally resistant to certain antibiotics. Penicillin, for example, does not affect the *Salmonella* species. But misuse of antibiotics has speeded up these natural processes, resulting in antibiotic resistant bacteria. This is an emerging issue for modern agriculture. The prudent use of these valuable products—in accordance with their terms of authorization and the manufacturers' recommendations—is essential in order to maintain their effectiveness.

The main concern is that a number of human pathogens have become resistant to antibiotics. It has been hypothesized that the transfer of resistant food-borne pathogens from livestock production are the cause. This paper examines the current evidence in this respect. In addition, Europe's response to public concern about antibiotic resistance is discussed.

Recent Scientific Evidence Of Sources Of Antibiotic Resistant Bacteria

Fourteen pathogens posing possible concerns in human medicine were discussed in a recent report (European Commission [EC], 1999). This report, which was commissioned by the European Commission's Consumer Affairs Directory, was drawn up by its Scientific Steering Committee. These key resistant pathogens are outlined in table 1 and include *Salmonella, E-Coli*, and *Streptococcus*. This report determined definitively that for the vast majority of these organisms there is no link between the emergence of resistant human pathogens and the use of antibiotics in the animal health sector.

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Table 1: Key Resistant Pathogens in Human Medicine.

Organism	Animal Source of Resistance?
Methicillin-resistant Staphylococcus aureus	NO
Mycobacterium tuberculosis	NO
Streptococcus pneumoniae	NO
Streptococcus pyogenes	NO
Neisseria meningitidis	NO
Neisseria gonorrhea	NO
Campylobacter spp	Possible
Salmonella spp	Possible
E coli (urogen, O157)	Possible
Vancomycin-resistant Enterococci	Possible
Pseudomonas aerugenosa	NO
Klebsiella spp	NO
Acinetobacter spp	NO
Enterobacter spp	NO

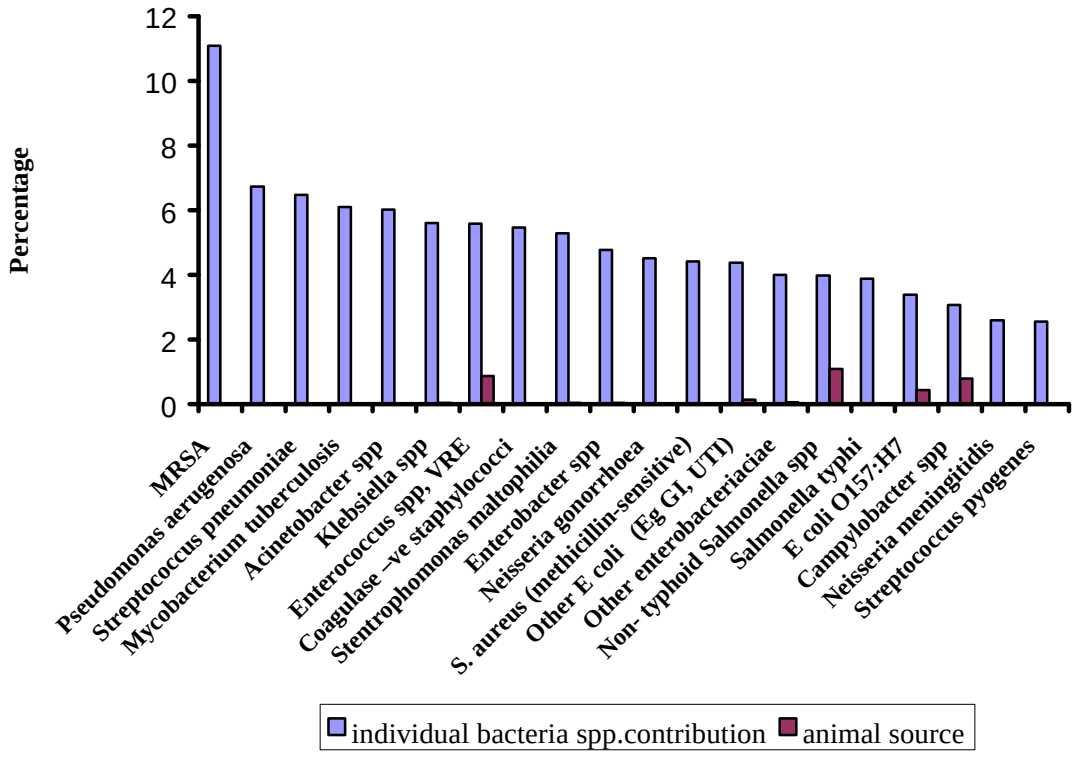
Note. From "Opinion of the Scientific Steering Committee on Antimicrobial Resistance," report by the European Commission, DG XXIV, Consumer Policy and Consumer Health Protection, 1999; and from "Antibiotic Growth Promoters, Villains, or Scapegoats?" by R.G. Bywater, 2000, paper presented at the Royal Society Medicine Meeting on Antibiotic Resistance, p. 2, table 1.

A study by Casewell (1998) at King's College Hospital, London examined the antibiotic resistance profiles of human and poultry *Vancomycin-resistant Enterococci* (VRE) isolates. Casewell (*ibid*.) found that while human and poultry strains possessed many common structural features, they represented two statistically distinct populations. Casewell (*ibid*.) concluded that the most plausible cause of VRE is cross-infection resulting from hospital-use of vancomycin and not cross-transfer from contaminated foods. Evidence implicating the transfer of resistance from animals to humans was lacking and, therefore, banning antibiotic feed additives is "most unlikely" to have any impact on the clinical problems being faced the human health sector. Casewell (*ibid*.) concludes,

> There is at present, in our view, a lack of evidence to indicate that there is a significant contribution of resistance from animals to humans…. The traditional clinical explanation for the appearance of antibiotic resistance in hospitals, namely, selection and the generation of resistance through clinical antibiotic use and cross infection, seems a more plausible explanation and cause for concern…. On the basis of present evidence, it seems most unlikely that banning feed additives would make any impact on the clinical scene.

Another study by Bywater and Casewell (2000) surveyed 20 hospital clinicians and microbiologists to determine which bacteria species are causing resistance problem in humans and where the resistance came from.

Figure 1: Contribution (%) of Individual Bacteria Species.



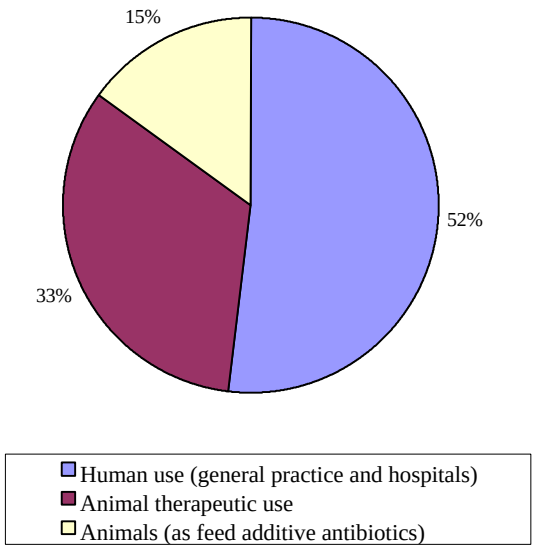
This was the first survey to quantify the relative impact of individual organisms on resistance, finding that MRSA (Methicillin Resistant Staphylococcus Aureus) is clearly the main problem in humans. Animal sources accounted for less than 4% of the human antibiotic resistance problem. The results of this questionnaire give an interesting view of the relative impact of antibiotic resistance along an important series of human pathogens, and they also suggest that animal sources contribute little to the overall problem. This study confirms earlier results by Casewell (1998) therefore.

European Demand For Antibiotics

Almost half of Europe's total consumption of antibiotics is by animals (see figure 2). While some resistance occurs in animals, it is in no way comparable with the level of resistance found in humans. If resistance to a particular product does became a major problem in the animal sector, the efficiency of that product would be seriously compromised and would eventually be abandoned by the veterinary profession. No antibiotic has ever been removed from the market due to resistance in animals. This raises the question of why animal pathogens are more responsive to antibiotic treatments? And why have antibiotics used widely in animals not been compromised by resistance problems?

One explanation to these questions lies in the patterns of antibiotic usage in animals and humans. Three times fewer antibiotics per kilo lightweight are used in animals than in humans for feed purposes. Since most of the antibiotics used in animal production are older, and therefore less potent than commonly used human drugs, volumes of the active ingredient used per treatment are also significantly higher in human treatments. Table 2 provides estimates of antibiotic sales volumes for animals within the EU by type of antibiotic. Fully two-thirds of sales are for *Tetracyclines*, an older antibiotic. The number of antibiotic treatments received by animals is far less than the number of treatments administered to the human population—by a ratio of 5 to 1.

Figure 2: Usage of Antibiotics in Human and Animals in the EU in 1997 (10,500 Tons of Active Ingredient at 100% Purity).



As for the balance of use between animals and humans, statistically it is more likely for a human to receive a greater number of antibiotic treatments over his or her lifetime. The average life expectancy for both women and men across the EU is well in excess of 70 years. When comparing this life expectancy with an average of 5-7 weeks for poultry, 6 months for pigs, and 2-4 years for beef cattle, more treatments are likely for the human population. Hence, greater exposure will encourage greater resistance in humans.

Table 2: European Veterinary Consumption of Therapeutic Antibiotics (1997).

Product Group	% Share
Penicillins	9
Tetracyclines	66
Macrolides	12
Aminoglycosides	4
Fluoroquinolones	1
Trimethoprim/sulphas	2
Others	6
Total[a]	100

[a] Total consumption is 2,494 tonnes of active ingredient at 100% purity. From "Survey of Antimicrobial Usage in Animal Health in the EU" by the European Federation of Animal Health (FEDESA), September 1998. Brussels: FEDESA.

In the most intensive livestock production sectors (often the most criticized sectors for resistance), comprehensive control methods are in place, which provide an important barrier to the development of antibiotic resistance. Most broiler chickens and fattening pigs are reared in "all-in" or "all-out" systems whereby entire flocks of birds or herds are moved out of rearing units. Housing is then thoroughly disinfected prior to the infiltration of the new stock, thereby reducing the transfer of bacteria to a new animal. With the potential of further complications and the expense of antibiotic use, if a specific antibiotic treatment does not achieve a cure, the infected animal is slaughtered. Again, this regime is in stark contrast to human treatments where antibiotics are often administered over long periods of time to the chronically ill. In cases where patients have lowered resistance to pathogens the complete elimination of pathogenic bacteria may never be achieved.

Industry Initiatives

As the risks to human and animal from resistance to antibiotics are extremely important to consider, a group of international organizations representing the animal health industry, the farmers, and the veterinarians (World Veterinary Association [WVA], International Federation of Agricultural Producers [IFAP], & the World Federation of Animal Health Industry [COMISA], 1999), have agreed upon a standard set of basic principles governing prudent antibiotic use. The following protocol is to be used in their administration:

- Antibiotic use should be subject to professional advice including that of the veterinary surgeon as appropriate.

- Veterinarians should use their professional judgment when selecting antibiotic therapies, balancing the risks and benefits involved for both humans and animals, and utilizing bacterial diagnosis and sensitivity tests whenever possible.

- Product label instructions should always be closely followed with respect to species and disease indications, dose regimes, withdrawal periods, and storage. Off-label use should

be undertaken only in exceptional circumstances, and always under veterinary surgeon control.

- Dose regimes should always be followed closely. Treatment should always be administered for a sufficient period to obtain a cure, but should be as short as possible in order to minimize exposure of the bacterial population to the antibiotic used.

- Records of all antibiotic administration should be kept. Efforts should be made to harmonize record-keeping requirements.

- Coordinated surveillance of antibiotic susceptibility should be conducted, with samples gathered at the farm and slaughterhouse levels, as well as in meat. Data should be made available to prescribers allowing them to optimize prudent use.

- Research into efficacious, scientifically proven alternatives to antibiotics should be undertaken, along with the impact of these alternatives on selection for resistance.

European Regulation Of Antibiotic Use In Animals

The European Union's recent precipitous ban on products that have been used safely and successfully as digestive enhancers is indicative of a general desire on the part of Europe's politicians to operate in a risk free environment. That desire has already placed a heavy burden on the animal health industry in terms of over-zealous regulatory demands. Now it threatens to deprive animals, their owners, and the industry of scientifically proven products.

In pursuit of zero risk, the authorities have increasingly focused on the "precautionary principle"--a concept that is used to justify the temporary withdrawal of products in exceptional circumstances, for example, where the safety of those products is in question. The precautionary principle allows more time for scientific research to be undertaken in order to answer questions about their perceived risks.

The precautionary principle was originally developed for use in the field of environmental protection. A "precautionary approach" is sanctioned in international trade agreements governing the application of health protection measures. The principle is not explicitly referred to in European law. However, existing regulations for the authorization and renewal of authorizations of veterinary products already take a precautionary approach.

The approval process for animal health products requires the generation of exhaustive trial data; scientific assurance of quality, safety, and efficacy prior to obtaining a marketing license; and a comprehensive system of post-marketing surveillance (called pharma-covigilance) after approval. Mechanisms enabling the swift withdrawal of products where health concerns are raised are also part of the existing regulatory framework (Vanhemelrijck, 1999).

Is A Ban Necessary?

More than 300 delegates from 30 countries convened at the 1999 Office International des Epizooties (OIE) and the United Nations Food and Agriculture Organization (UN FAO) conference on animal health and food safety held in March 1999. The main topics of concern at the conference were the use of antibiotics in animals and ensuring the protection of public health

(see OIE, 1999). The participants focused on the development of recommendations in three main areas:

1. The prudent use of antibiotics in animals;
2. Monitoring and surveillance of antibiotic resistance; and
3. To develop models enabling proper risk/benefit assessment.

Significantly, the conference recommendations on risk assessment and the use of the precautionary principle implied criticism of the EU 1998 ban on food additive antibiotics. The conference concluded, for example, that the scientific knowledge is not sufficient to give a proper assessment of the risks associated with antibiotic use in animals.

Science Or Politics?

European politicians and regulators have important decisions to make. In this decision making process politics can dominate. Two recent reports offer a stark illustration of the contrast in the use of scientific and political logic to arrive at a decision. The European Medicine Evaluation Agency's (EMEA) Committee for Veterinary Medicinal Products (CVMP) wrote one of the reports (CVMP, 1999). The other report was written by the European Commission DG XXIV Scientific Steering Committee (EC, 1999). This second report examined the issue of antibiotic resistance for both animals and humans. The two reports reach three broadly similar conclusions:

1. There is not sufficient evidence to identify the cause of resistance emergence;
2. There is a need for closer monitoring of antibiotic use; and
3. There is a need for closer surveillance of resistance.

Some differences did arise, however, in these reports. The CVMP called for the development of programs to assess antibiotic resistance in animals and the potential for transfer to humans. In contrast, while the scope of its investigation was supposed to cover use in human medicine, crop protection, and animal health, the Scientific Steering Committee's report demanded immediate action almost exclusively in the animal health sector. The Committee concluded that it may take several years to quantify the economic contribution of antibiotic use in the animal sector, or potential risks resulting from their use. Hence, the Committee argued it would be better to act now by banning the products in the animal sector and then observing whether or not the ban had any effects on antibiotic resistance.

Concluding Comments

The main decision that needs to be made in the animal health sector is whether or not science is more important than politics. The EU precautionary principle has become a leading issue in the argument of whether or not to ban antibiotic use. In the future, it will be necessary to weigh the potential risks of using the antibiotics against the potential benefits of being able to freely use treatments (EMEA, 2000). Risks of resistance are scientifically inconclusive after much experimentation. One can make a case that the European habit of banning antibiotic products is politically motivated rather than scientifically based.

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