9. Antimicrobials as growth promoters: resistance to common sense

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9.1. Introduction

An antibiotic is defined as a substance produced by microorganisms that inhibits or kills other microorganisms. Synthetic antimicrobial substances are referred to as chemotherapeuticals. The word 'antimicrobial' (as a noun) is often used to encompass any substance of natural, semi-synthetic or synthetic origin that kills or inhibits the growth of a microorganism.

The antimicrobial era began in 1910 with the introduction of Salvarsan into the therapy of syphilis and expanded in the 1930s when the first chemotherapeuticals (sulphonamides) made their way into clinical use in human medicine. The antibiotic, penicillin, was discovered by Alexander Fleming (Fleming, 1929) but was not introduced for therapy until 1941. Shortly after its introduction for use in humans, penicillin was used in animals for the treatment of various bacterial diseases.

Antimicrobials are probably the single most important discovery in the history of medicine. They were considered miracle drugs. Over the years they have saved millions of lives by killing bacteria that cause some of the worst infectious diseases in man and animals.

9.1.1. Antimicrobials for growth promotion

The growth promoting properties of antimicrobial agents in farm animals were discovered in the late 1940s. Trials where fermentation waste from tetracycline production was fed to chickens as a source of vitamin B^{12} revealed that the chickens fed the waste grew more rapidly than did the controls. It was soon found that this effect was not due to the vitamin content of the feed but to residual tetracycline (Stokstad and Jukes, 1949). The practice of feeding sub-therapeutic doses of antimicrobials over long periods of time was readily adopted and soon became an integrated part of the production systems developed in industrialised animal husbandry. Apart from increased growth rate and/or increased feed conversion, examples of other observed effects of antimicrobials at low doses are improved egg production in laying hens, increased litter size in sows and increased milk yield in dairy cows.

Antimicrobial growth promoters are freely accessible and sold over the counter, while antimicrobial drugs for therapy in most cases are available on prescription only. The use of antimicrobial growth promoters over four decades has undoubtedly contributed to the development of current animal production systems. Use of antimicrobial growth promoters apparently provides some protection against certain diseases promoted by intensification and allows, for example, unphysiological early weaning and high stocking rates, raising questions on animal ethics and animal welfare.

9.1.2. Development of resistance

Most antimicrobials are produced by microorganisms and existed long before they were used as medicinal drugs. Microorganisms produce antimicrobial substances to kill other microorganisms in order to create a foundation for their own survival and propagation. The bacteria exposed to antimicrobials develop strategies for survival; development of resistance is one such strategy. This follows the classical concept of survival of the fittest and it is thus not surprising that antimicrobial resistance has probably existed for as long as have bacteria.

Concern about penicillin resistance more or less accompanied its introduction as a medical drug in the early 1940s. The discoverer of penicillin Alexander Fleming, in a newspaper interview by the *New York Times* (1945), warned that misuse of penicillin could have the result that 'microbes are educated to resist penicillin'. Increasing resistance was noted in several important bacteria known to cause infectious disease. By the early 1950s the problem of antimicrobial resistance was well acknowledged in the medical, veterinary and pharmaceutical press.

Originally it was thought that acquired resistance in a bacterium only occurred through mutation in existing genes, which would mean that the resistance trait would be confined to the mutant clone and spread of resistance confined to that clone (vertical transmission). In the 1960s it was shown that resistance, in addition to mutation, could also be developed through the uptake of existing genes. In this case, the resistance trait through mobile genetic elements can also spread to other bacterial clones, to other bacterial species and even to other genera (horizontal transmission) (for a review see, for example, Amabile-Cuevas and Chicurel, 1992).

9.2. The first early warning

9.2.1. The Swann Committee

In the mid-1960s growing concern over food-borne infections with multi-drug-resistant salmonella in the United Kingdom led the government to establish an independent advisory committee in 1968. The task of the committee, chaired by Professor Michael Swann, was to examine the issue of transferable antimicrobial resistance and the consequences for human and animal health arising from the use of antimicrobials for growth promotion and in veterinary medicine. The Swann Committee (Swann, 1969) judged the data available 'a sufficiently sound basis for action' and the principal recommendations on antimicrobial growth promoters were that: 'permission to supply and use an antibiotic without prescription for adding to animal feed should be restricted to the antibiotics which:

- are of economic value in livestock production under United Kingdom farming conditions;
- have little or no application as therapeutic agents in man or animals;
- will not impair the efficacy of a prescribed therapeutic antibiotic or antibiotics through the development of resistant strains of organisms.'

Recommendations on specific drugs were also included, for example: 'tylosin should not be available without prescription for use as a 'feed' antibiotic.'

Another recommendation was the establishment of a single permanent committee which 'should have overall responsibility for the whole field of use of antibiotics and related substances whether in man, animals, food preservation, or for other purposes'.

9.3. Subsequent action or inaction

9.3.1. Implementation and dilution of the Swann Report

The recommendations in the Swann Report were based on less than full scientific certainty and created much debate and cries for more research, and faced strong opposition from the pharmaceutical industry and farming community in the United Kingdom. But most of the main recommendations were adopted in the United Kingdom and later on in the European Union (EU).

However, subsequent governments in the United Kingdom gradually diluted the recommendations of the Swann Report. The recommendation to establish an overarching, strong and permanent committee responsible for the whole field of antimicrobial usage was not fully implemented. For example, no epidemiological studies to monitor antimicrobial resistance development were set up.

Against the Swann recommendations, the EU accepted the macrolides tylosin and spiramycin as growth promoters in 1975. This has probably been one of the major reasons for the widespread macrolide resistance in, for example, enterococci and campylobacter from pigs. Use of the antimicrobial growth promoter avoparcin was extended to other species, such as adult cattle, against the Swann recommendations and its use increased from the mid-1970s at about the same time that its medical equivalent, vancomycin, started to come into hospital use.

One of the scientific arguments put forward to support this use of antimicrobials for growth promotion was that the low dose presents a special case in selecting for resistance. For example, Walton (1988) stated: 'In practical terms the use of a sub-lethal or a sub-inhibitory antibiotic concentration is therefore unable to select resistant strains from a bacterial population, and in this respect the Swann Report's conclusion and recommendations were in error.' However, the recent bans on avoparcin, virginiamycin and tylosin followed the publication of studies demonstrating that

this view (Walton's amongst others) was wrong.

Worldwide, there are great differences in the regulatory control of antimicrobials for therapy, prophylaxis and growth promoting purposes. In some countries, such as the United States, low doses of tetracycline and penicillin are still used as feed additives for prophylaxis and growth promotion without veterinary prescription, while therapeutic antimicrobials are often prescription-only medicines.

9.3.2. The Swedish ban

Similar to the situation in other countries, some Swedish scientists viewed the practice of routine addition of antimicrobials to animal feeds with scepticism. Following the recommendations of the Swann Committee in the United Kingdom, a broader debate was initiated, which eventually led to a reassessment of the use of antimicrobials as feed additives (LBS, 1977).

A working group of the Board of Agriculture concluded, among other things, that: 'the use of antibiotic feed additives entails a risk of increased resistance in bacteria but as the substances in use are mainly active against gram-positive bacteria from which resistance is not transferred, the impact of such development is negligible.' On the other hand, a negative attitude to all kinds of additives among consumers was noted by the group. The benefits, in terms of increased production and prevention of certain diseases, were also acknowledged (LBS, 1977). Legislative changes, especially in the requirements for approval, were proposed in order to mitigate possible risks.

At the same time, farmers were growing increasingly sceptical towards feed antimicrobials. They were concerned that the continued use of antimicrobials might harm consumer confidence. The Federation of Swedish Farmers (LRF) made a policy statement, declaring that Swedish agriculture aimed towards a more restricted and controlled use of antibiotics. In a letter to the Ministry of Agriculture in 1984, the LRF requested a ban on the use of antibacterials as feed additives.

In response to the above, the Ministry of Agriculture drafted a new Feedingstuffs Act (Government Bill 1984/85). Among other things, the draft proposed that the use of antimicrobials in feed should be restricted to treatment, prevention or cure of diseases, meaning that their use for growth promotion should not be allowed. The basis cited for this amendment was the risk of increased resistance, especially the risk of cross-resistance to other substances and the risk of increased susceptibility of animals to salmonella and other enteric pathogens. The government also stressed that 'there is uncertainty on the long-term effects of the continuous use of feed containing chemotherapeutics' (Government Bill 1984/85).

The Feedingstuffs Act was passed by parliament in November 1985 and came into force in January 1986. Since then antimicrobials, whether in feed or administered otherwise, have only been allowed for therapy and on veterinary prescription, and as a result the total consumption of antimicrobials was greatly reduced from around 50 tonnes in 1985 to around 20 tonnes in 1996 (SOU, 1997).

During the accession negotiations with the EU, Sweden was granted a temporary derogation from European legislation concerning the use of antibiotics as growth promoting feed additives. In support of the Swedish view the Ministry of Agriculture appointed a commission to collect and review scientific data on antibiotic growth promoters. In 1997 the commission presented its report and among other points noted that 'antimicrobial feed additives can at levels permitted in feeding stuffs, be used for treatment or prevention of animal disease, which is in violation of Council Directive 70/524/EEC' (SOU, 1997). According to this directive, as amended in 96/55/EEC, Article 3a, authorisation of an additive shall be given only if at the level permitted, treatment or prevention of animal disease being excluded.

The commission concluded that 'the risk for increased resistance associated with the general use of antibiotic growth promoters is far from negligible and the potential consequences are serious for both animal and human health' (SOU, 1997).

The magnitude of the risk is difficult to fully establish because of the complexity of the problem and the lack of pertinent data. The report outlined the research required to be undertaken in a 17-step causal chain, assessed the minimum time required to undertake the research to be 5–10 years, and also that the

research had to be undertaken for each resistance gene and for each antimicrobial substance, with subsequent updates of the risk assessment.

The report went on to ask who would bear the costs of waiting to do further research, or of taking action then to restrict antimicrobials — the risk-maker or the risk-taker? The commission finally urged: 'As the risks involved are of uncertain magnitude, the decisions on risk management are particularly difficult. The risk can obviously not be excluded with certainty, nor can it be determined as acceptable. Scientists may declare that the information is inadequate for decision making, but for the policymakers, failure to take action is not a neutral position but represents a positive decision to do nothing. In a climate of uncertainty it is preferable to show caution.' (SOU, 1997)

9.3.3. The ban of avoparcin

In March 1995 , when the first information on the occurrence of avoparcin- and vancomycin-resistant enterococci in pigs and poultry had become available (Klare *et al.*, 1995; Bates *et al.*, 1994; Aarestrup, 1995), the Danish farmers' organisations agreed with the feeding industry that there would be a voluntary cessation in the use of avoparcin in animal feed to reduce the spread of antimicrobial resistance. This was followed by a governmental ban implemented on 20 May 1995 and reported to the European Commission as requested by the safeguard clause of Council Directive 70/524/EEC. According to this a Member State can, as a result of new information, temporarily suspend the use of an approved feed additive if its use constitutes a danger to animal or human health.

The scientific background for the Danish ban was the demonstration:

- of cross-resistance between avoparcin and vancomycin;
- that the resistance is transferable;
- that the use of avoparcin as a growth promoter selects for vancomycin-resistant enterococci and that vancomycin-resistant enterococci can be transferred to humans via the food chain (DVL, 1995).

In Norway the use of avoparcin was suspended in June 1995, and in Germany the government issued a ban on avoparcin in January 1996.

In May 1996 the EU Scientific Committee on Animal Nutrition (SCAN) concluded that further evidence was required to establish a risk to human health, animal health or the environment caused by avoparcin. However, the committee accepted that serious questions concerning the safety of avoparcin had been raised and stated that the feed-additive use of avoparcin should be reconsidered at once if it were shown that transfer of resistance was possible from animal to human. The European Commission, however, proposed that in the climate of uncertainty and to avoid taking any risk, a temporary ban should be placed on the use of avoparcin as a feed additive in all EU Member States. This was agreed by a qualified majority vote of the Standing Committee on Feedingstuffs in December and the ban came into force on 1 April 1997.

9.3.4. Danish ban of virginiamycin

On 16 January 1998, the Danish government banned all use of virginiamycin as a growth promoter in Denmark, due to a risk of selection of streptogramin-resistant enterococci in pigs and poultry (Aarestrup *et al.*, 1998). The step was taken to protect human health and to preserve the lifespan of Synercid, which was then undergoing hospital trials but which has now been licensed for the treatment of certain multi-drug-resistant infections in humans.

9.3.5. EU bans four antimicrobial growth promoters

On 14 December 1998, the agriculture ministers of the EU Member States voted in favour of a proposal to ban the use of four antimicrobial growth promoters from July 1999: virginiamycin, bacitracin zinc, tylosin phosphate and spiramycin. The ban was submitted by the European Commission as 'a precautionary measure to minimise the risk of development of resistant bacteria and to preserve the efficacy of certain antibiotics used in human medicine'. The pharmaceutical industry protested against the decision and called for further scientific facts about the risks involved in the use of antimicrobial growth promoters. Afterwards, the decision was challenged before the European Court of Justice by the manufacturer of virginiamycin, who called for an annulment of the entire decision. Final ruling in the case is not expected before the end of the year 2001.

9.3.6. Avilamycin

The latest example of an antimicrobial growth promoter from the EU list of approved products showing cross-resistance with a potential human drug (everninomycin) is avilamycin (Aarestrup, 1998). However, the manufacturers of everninomycin have recently withdrawn it from hospital trial worldwide.

9.3.7. Scientific reports and recommendations

In 1997 the World Health Organization (WHO) organised a scientific meeting which addressed the medical impact of the use of antimicrobials in food animals. The meeting concluded that 'the magnitude of the medical and public health impact of antimicrobial use in food animal production is not known' (WHO, 1997). The recommendations from the meeting stated: 'Increased concerns regarding risks to public health resulting from the use of antimicrobial growth promoters indicate that it is essential to have a systematic approach towards replacing growth promoting antimicrobials with safer non-antimicrobial alternatives.'

The Invitational EU Conference on The Microbial Threat held in Copenhagen, Denmark, in 1998, reached a similar conclusion and stated: 'Most of those at the conference considered the use of antimicrobials for growth promotion was not justified and that it was essential to have a systematic approach towards replacing growth promoting antimicrobials with safer non-antimicrobial alternatives including better farming practice.' (The Copenhagen Recommendations, 1998)

The conference was organised by the chief medical officers of the EU Member States and included both medical and veterinary authorities and researchers, representatives of farmers' organisations, the pharmaceutical industry and the animal feed industry.

Because of concern over the implications for human and animal health of the rapidly increasing rate of development of antimicrobial resistance, the European Commission (DGXXIV) asked the Scientific Steering Committee (SSC) to evaluate the current position regarding the prevalence and development of antimicrobial resistance, and to examine its implications for human and animal health, particularly with regard to the development and management of infections. In 1999 the SSC concluded in its report that 'action needs to be taken promptly to reduce the overall use of antimicrobials in a balanced way in all areas: human medicine, veterinary medicine, animal production and plant protection' (SSC, 1999). In relation to antibiotics for animal growth the SSC recommends that 'the use of agents from classes which are or may be used in human or veterinary medicine should be phased out as soon as possible and ultimately abolished'.

In the newly issued 'Global Principles for the Containment of Antimicrobial Resistance due to Antimicrobial Use in Animals Intended for Food', WHO recommends that the use of antimicrobial growth promoters that belong to classes of antimicrobial agents used (or submitted for approval) in humans should be terminated or rapidly phased out in the absence of risk-based evaluations (WHO, 2000).

9.4. Advantages and disadvantages of the use of growth promoters

Over the entire period during which antimicrobial agents have been used as growth promoters there has been great emphasis on the advantages of these feed additives as a means to improve farm animal production and productivity. Much less attention has been directed towards possible side-effects, and the number of independent scientific studies is relatively small compared to studies and congress contributions supported by the pharmaceutical industry.

Not until recently, when the occurrence of vancomycin-resistant enterococci in animals was found to be associated with the use of avoparcin as an additive to animal feed and the possible consequences for human health were made clear, did the number of independent research studies dealing with these aspects increase significantly.

In the last few years substantial scientific evidence has shown that the use of antimicrobial growth promoters in food animals contributes to the problems of antimicrobial resistance in humans. This has most convincingly been shown for vancomycin-resistant enterococci.

Although the widespread use of antimicrobials in human medicine undoubtedly is of more importance for the emerging antimicrobial resistance problems

in humans, this cannot justify ignorance of potential human health risks related to the use of antimicrobials in food animals. The continuous use of antimicrobials in feed is one of the major sources of overuse and misuse of antimicrobials in animal farming.

This ongoing debate has made it clear that the usage of antimicrobial agents as feed additives is a complex issue, with implications not only for human and animal health but also for animal welfare, food safety, environmental aspects and for the development of production systems, feeding practices and management. Some of the positive and negative effects of antimicrobial growth promoters are listed in Table 1.

9.5. Conclusions and lessons for the future

The original early warning in the Swann Report on the risk of antimicrobial resistance spreading amongst animals, and from animals to humans, was based on a low level of scientific proof, but on a competent microbiological assessment that foresaw possible adverse consequences of the continuous use of therapeutic antimicrobial agents in animal feed. The recommendations were clearly precautionary, although the word 'precaution' was not actually used in the Swann Report.

Subsequent scientific research, developed primarily during the 1990s, has shown that transferable resistance is not restricted to certain bacteria (gram-negative), but is much more widespread within the microbiological universe, and that genes can easily move not only between closely related bacterial species, but also even between genera. These results confirm that the Swann Report was both accurate in its evaluation of data at the time and far-sighted in its assessment of future trends.

The justification for the later dilution of its conclusions and compromises on its recommendations was based mainly on narrow considerations of what was precisely known rather than on taking account of what was not known, of the ignorance within the field and the possible consequences for widespread antimicrobial resistance. In other words science that embraces complexities, uncertainties and unknowns with more humility and less hubris is needed.

Furthermore, scientific committees which are responsible for the evaluation of confidential information from industry, should consist of a broad panel of independent and up-to-date experts, with relevant expertise and experience from all of the disciplines that are implicated in a broad assessment of the risks, benefits and technological options involved. In this case, expertise from human medicine would have been particularly valuable for every risk assessment.

The experience from this case suggests that assessments of risk need to be much wider, taking into account both positive and negative impacts, the long-term microbiological and ecological effects on human and animal health and the environment, and alternative options, such as better animal husbandry (see Table 9.1.).

As the risks involved are of uncertain magnitude, the decisions on risk management are particularly difficult. The risk can obviously not be excluded with certainty, nor can it be determined as acceptable. In a climate of uncertainty it is preferable to show caution. In this situation decision-making needs to involve precaution, particularly when it is unacceptable, inhuman and unethical to wait for ultimate proof, when human fatalities could be involved.

Another clear lesson from this case study is that stakeholders other than regulatory bodies, such as the farmers and their organisations, can take voluntary steps in advance of legislation to stop the use of products which cause concern and loss of confidence amongst consumers. In this case they, as well as the Swann Committee, have been vindicated by history. Common sense and far-sighted use of good scientific evidence which can predict serious impacts should not be ignored whilst waiting for ultimate proof.

Positive and negative effects of antimicrobial growth promoters on some broad issues of animal production Table 9.1.

Broad issue	Positive effect	Negative effect
Animal health	Certain diseases — primarily enteric — may be controlled to some extent	Limits treatment possibilities due to development of antimicrobial resistance; masks sub-clinical disease and infection; limits incentives for hygienic improvements
Human health	None	Transfer of resistance to humans with increased societal costs for health care; shortens economic life of medical antimicrobials; occupational hazards through exposure to aerosol and dust contaminated with antimicrobials
Animal welfare	Alleviates and dampens signs of disease	Camouflages stress associated with sub-clinical disease; allows higher stocking rates
Environment	Better utilisation of animal feed; less manure	Increases the environmental pool of antibiotic resistance genes; antibiotic residues
Animal husbandry	Increased production and improved productivity	Stimulates increased intensification of animal production
Production system	Lower labour demand due to possibility of more intense production methods	Hampers the development of animal-friendly production systems
Animal feed	None	Camouflages bad feed quality; hampers improvements in feed formulation and development of alternatives

Source: L-E. Edqvist and K. B. Pedersen

Antimicrobials: early warnings and actions Table 9.2.

1945	Alexander Flemming warns against misuse of penicillin as 'microbes are educated to resist'
1950s	Antibiotic resistance widely recognised — vertical transmission.
1960s	Horizontal transmission recognised
1969	Swann Committee recommends severe restrictions on antimicrobials in animal feed
1970s	Most Swann recommendations initially implemented in the United Kingdom and EU
1975	Swann recommendations are relaxed: tolysin and spiramycin still permitted as growth promoters as human equivalents; vancomycin comes into use
1977	Swedish Agriculture Board considers potential risk of antibiotic resistance, but concludes it is negligible
1984	Swedish farmers ask for government ban on antimicrobials in animal feed because of health and consumer concerns
1985	Swedish ban on grounds of antibiotic resistance in animals and 'uncertain' long-term effects
1997	Swedish report concludes that risk of antibiotic resistance in humans is 'far from negligible'
1997	WHO scientific meeting concludes that it is 'essential to replace growth promoting antimicrobials'
1998	EU bans four antimcirobials in animal feed as 'precautionary' measure.
1999	EU Scientific Steering Committee recommends phase-out of antimicrobials that may be used in human/animal therapy
1999	Pharmaceutical industry opposes EU bans and takes EU to the European Court; judgement expected end 2001
2000	WHO recommends ban on antimicrobials as growth promoters if used in human therapy and in absence of risk-based evaluation.

Source: EEA

9.6. References

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