

Public Health Risks: Antibiotic Resistance - Review -

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ABSTRACT : Antibiotic resistance in human pathogens is a major public health issue. Some of the resistance problem can be attributed to the transfer of resistant bacteria from animals to people and the transfer of resistance genes from animal pathogens and commensal bacteria to human pathogens. Control measures include improvements in food hygiene to reduce the spread of zoonotic bacteria to people via the food chain. However, to specifically address the issue, the medical profession must control misuse and overuse of antibiotics in hospitals and community practice. In addition, the livestock industries and their advisors must reduce and refine the use of antibiotics in animal production and replace antibiotics with alternative disease control measures as much as possible. (*Asian-Aust. J. Anim. Sci.* 2001. Vol. 14, No. 3 : 414-422)

Key Words : Antibiotic Resistance, Growth Promotant, Enteric Bacteria, Public Health, Animals

INTRODUCTION

Resistance to antibiotics is one of the most serious global medical problems as we enter the 21st Century. Although resistance was recognised soon after antibiotics were introduced little effective action has been taken. Medical authorities are already confronted with infections for which no antibiotic is effective because the causative bacteria have acquired resistance to all available antibiotic agents. This is largely the result of over-use and misuse of antibiotics in hospitals and the community generally. However, one of the issues receiving close attention at the moment is the link between use of antibiotics in animals and the development of resistance in human pathogens. There is evidence that resistance in some human enteric pathogens has arisen because of transfer of resistant bacteria or resistance genes from animals to people via the food chain (Barton, 2000).

ISSUES FOR THE LIVESTOCK INDUSTRIES

Response to the resistance problem

Attention to possible adverse effects to human health first received worldwide coverage with the release of the Swann Report (1969). This report concluded that there probably was a hazard to human health from feeding sub-therapeutic levels of antibiotics to food producing animals (as is the case with growth promotants). The committee recommended that

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** This paper was presented at 2000 APEC China Seminar on Public Health Issues in Animal Production/Animal Products which was held on October 15~19, 2000 in Beijing, P. R. China.

antibiotics for growth promotant use should be restricted to compounds not used therapeutically in man or animals and which did not select for resistance to such compounds.

There was some response to these recommendations in many countries and in 1986 Sweden banned the use of antibiotic growth promotants (CAFA, 1997). There was vigorous debate in Europe and Scandinavia about the validity of the Swedish decision, with authorities in other countries disputing the merits of decision. Claims were made that it resulted in an overall increase in the use of antibiotics because of increases in diseases that would otherwise have been prevented by the action of the growth promotant antibiotics (Viaene, 1997a, b, c). Sweden has consistently provided evidence supporting their action, both in terms of reduction in antibiotic use and improvements in health status of their herds and flocks (Wierup, 2000).

In 1995 Aarestrup and co-workers in Denmark reported the isolation of vancomycin resistant enterococci (VRE) from pigs and chickens fed avoparcin (a glycopeptide antibiotic very similar to vancomycin) (Danish Veterinary Laboratory, 1995). The immediate conclusion was that this accounted for the very sudden and rapid increase in VRE seen in some countries over the preceding 5 to 10 years. As a result of this and despite the lack at the time of convincing scientific evidence, the EU eventually moved to ban the use of a number of commonly used growth promotant antibiotics as a precautionary action.

Concurrently with this there were enquiries in a number of countries addressing the issue of a link between antibiotic use in animals and the development of resistance in human pathogens (WHO 1997, 1998; MAFF, 1998; JETACAR, 1999).

Resistance problems in human pathogens

The majority of human antibiotic resistance problems have no connection with use of antibiotics in animals with problems occurring in both hospital and community settings (Gold and Moellering, 1996; Collignon 1997). The most serious hospital problem is methicillin resistant *Staphylococcus aureus* (MRSA) (which is now an emerging community problem as well in some countries). Large scale use of vancomycin occurred particularly in the USA (Kirst et al., 1998) in response to the emergence of MRSA and this presumably led to the emergence and predominance of vanB VRE in that country, as avoparcin is not registered for use in the USA. In northern Europe and Scandinavia VRE is much less a problem because there is much less MRSA. However, the vanA VREs were readily detected in the faeces of healthy people in the community and these appear to have originated from use of avoparcin in pigs (van den Bogaard and Stobberingh, 2000).

Another hospital problem is extended spectrum β -lactamase producing Gram-negative bacteria (ESBLs) which have emerged as opportunist Gram-negative bacteria colonising hospital environments. Neither MRSA nor ESBLs have any connection with use of antibiotics in animals.

Serious and widespread community resistance problems which have developed because of over-use and misuse of antibiotics in people include penicillin-resistant pneumococci and multi-resistant *Mycobacterium tuberculosis*. Again these community problems are unrelated to use of antibiotics in animals.

Issues for animal industries

Antibiotics are very important in animal production for a number of reasons. Firstly, they are required on animal welfare grounds: if we use animals for food or fibre we have a responsibility to treat them if they are sick and to use antibiotics strategically to control and prevent disease if vaccines and other alternatives are not available. Secondly, there are economic grounds: use of antibiotics at sub-therapeutic levels (growth promotants) has a role in improving growth and production, particularly where hygiene and disease control is less than optimum. There is evidence from Europe and Scandinavia that where hygiene and disease control regimes are of a high standard there is no reduction in production if growth promotant antibiotics are not used (A.E. van den Bogaard, pers. comm.). However, others do not agree with this view (Lawrence, 1997; McOrist, 1997). Thirdly, there are public health grounds: some argue that use of antibiotics reduces excretion of zoonotic organisms such as salmonella (Gustafson and Bowen, 1997) but others argue that in fact use of antibiotics prolongs excretion (Corpet, 1996). Fourthly, there are reports

that some of the growth promotants are effective in controlling necrotic enteritis in chickens and swine dysentery and porcine proliferative enteropathy (Taylor, 1999).

Therapeutic use of antibiotics generally involves treatment of individual or small groups of animals with higher doses of antibiotics for a relatively short period whereas prophylactic use can involve treatment of quite large groups of animals for extended periods of time with moderate doses of antibiotics. Growth promotant use involves use of sub-therapeutic doses of some recognised antibiotics (e.g., tylosin, avoparcin, virginiamycin) or compounds with poorly defined antibacterial activity (e.g., ionophores) for very long periods, perhaps even for the entire life of the animals.

Resistance to antibiotics emerges as a response of the exposure of bacterial populations to those antibiotics. Over-use and misuse of antibiotics therapeutically has driven the resistance problem in human medicine whereas it would seem that prophylactic use to some extent and growth promotant use in particular have contributed most to the emergence of resistant bacteria in animals (van den Bogaard and Stobberingh, 1999; Barton, 1998). A study comparing enteric bacteria collected before commercial application of antibiotics commenced with currently isolated strains has shown that the former are sensitive and 20% of the latter demonstrate high level resistance to at least one antibiotic (Houndt and Ochman, 2000). In addition, low-level resistance genes were much more common in contemporary strains.

Development and persistence of resistance

In human medicine, *Staphylococcus aureus* resistant to penicillin were recognised as a clinical problem in 1954, 14 years after its introduction in 1940; methicillin resistant *S. aureus* emerged in 1968, 8 years after its introduction in 1960; and gentamicin resistance in *Pseudomonas aeruginosa* in 1968, 4 years after its introduction in 1964. A similar pattern is seen with veterinary isolates: for example, tetracycline resistance was reported in *E. coli* and salmonella in the 1950s (Smith and Crabb, 1957; Anderson, 1968), shortly after in-feed use became a common practice; and apramycin resistance was found in *E. coli* and salmonella within 2 years of its introduction to veterinary use (Wray et al., 1986).

Resistance genes are presumably present somewhere in the bacterial population before exposure to antibiotics. Abraham and Chain (1940) described β -lactamase production in *S. aureus* well before resistance became an issue. Similarly the early 1960s reports on R-plasmids in enteric Gram-negative bacteria (Watanabe, 1963) highlighted the potential for existence of resistance genes on mobile pieces of

DNA rather than the actual problems we now face.

Development and persistence of resistance is quite variable when one compares classes of antibiotics and species of bacteria. Some organisms appear to become resistant quite readily whereas others do not. For example, resistant strains of *Salmonella* Typhimurium emerge rapidly after exposure to antibiotics, whereas *Salmonella* Dublin remains relatively sensitive when exposed to the same antibiotics (MAFF, 1998). Penicillin resistance became a problem in *S. aureus* shortly after its introduction, but it took more than 20 years to appear in *Streptococcus pneumoniae* and is still not found in b-haemolytic streptococci. Resistance to fluoroquinolones in campylobacters (Jacobs-Reitsma et al., 1994) and apramycin in *E. coli* and salmonella (Wray et al., 1986) emerged very quickly following the introduction of these antibiotics into veterinary medicine whereas resistance to ampicillin appeared much more gradually (Linton et al., 1988). There are also differences between hosts - methicillin resistance rapidly emerged in human strains of *S. aureus* within a short time after its introduction, but bovine strains remain largely sensitive even after 30 years use as a mass-medication in dairy cows at the end of lactation.

There are many reports of the persistence of tetracycline resistance long after the withdrawal of the drug (Smith 1973; Hinton et al., 1984) whereas there is evidence from Denmark and the Netherlands that resistance to avoparcin declines quite rapidly once use of that antibiotic ceases (Bager et al., 1999). However, it has been postulated that re-exposure to previously withdrawn antibiotics will lead to a rebound effect, with very rapid re-emergence of resistance (Salyers and Amábile-Cuevas, 1997).

Antibiotic resistance in animal isolates of bacteria

There has been little systematic study of resistance in animal isolates of bacteria, except for salmonella and *E. coli*. Until the 1997 WHO meeting which discussed the medical impact of use of antibiotics in animals on human health, there was little interest in monitoring or surveillance of antibiotic resistance in animals. Over the last 5 years a number of countries have moved to establish such programs (WHO, 1999). The best developed of these is the DANMAP program in Denmark (Aarestrup et al., 1998).

E. coli: Generally speaking, *E. coli* is the best-studied organism. In herds or flocks treated with tetracycline, aminoglycoside and sulphonamide, widespread resistance is seen (Williams Smith, 1980; Wray et al., 1993a; Aarestrup et al., 1998). However, resistance to other antibiotics such as ampicillin and olaquinox is less widespread (Linton et al., 1988; Dunlop et al., 1998a, b). Following the introduction of fluoroquinolones, resistance to that class of antibiotics has been reported (Blanco et al., 1997; Heutin-Le

Corre et al., 1999). Multiple resistance to more than one class of antibiotics appears to be the rule with animal isolates of *E. coli*.

Salmonella spp: Because salmonella is a recognised food borne pathogen, a number of the published reports of resistance patterns in animal isolates have been linked with studies of human isolates (Threlfall et al., 1993; Seyfarth et al., 1997) or with concerns about resistance to particular antibiotics (Wray et al., 1986; Heutin-Le Corre et al., 1999). Salmonella was the first organism to be included in surveillance and monitoring studies (Wray et al., 1993b; Seyfarth et al., 1997; CAFA, 1997; Aarestrup et al., 1998; Fedorka-Cray et al., 1998). The failure to distinguish between different serovars of *Salmonella enterica* limits the value of these reports as some serovars such as Typhimurium are much more likely to be resistant than other serovars such as Dublin and Enteritidis PT4 (MAFF, 1998). In general it seems that resistance is generally less prevalent than in *E. coli* but that resistance to tetracyclines, sulphonamides and streptomycin is quite widespread.

Campylobacter: There are few reports on antibiotic resistance in enteric campylobacter as these organisms are not pathogens in animals and human infections rarely require treatment. Erythromycin-resistant campylobacters have often been reported, particularly *Campylobacter coli* (Moore et al., 1996). Aarestrup et al. (1997) found that tetracycline resistance was more common in human than pig or poultry isolates and that there was more macrolide and streptomycin resistance in isolates from pigs in comparison with human and poultry isolates. Resistance to a range of antibiotics has been reported in other studies (Lucey et al., 2000; Saenz et al., 2000).

Enterococci: Enterococci are also enteric commensal bacteria in animals. The detection of vancomycin resistant *E. faecium* in pigs and poultry fed avoparcin (Danish Veterinary Laboratory, 1995) provoked much interest and debate about the role of animal use of avoparcin in the development of vancomycin resistant enterococci (VRE) in people (Klare et al., 1995; Aarestrup et al., 1996; Jensen et al., 1998a; Kruse et al., 1999). Investigations into resistance to other antibiotics of interest (or potential interest) in human medicine led to the discovery of resistance to virginiamycin (Hammerum et al., 1998) and avilamycin (Aarestrup, 1998) and the potential for the impact of this on use of related antibiotics in human medicine is still hotly debated. Resistance has also been reported in enterococcal isolates from animals to the macrolide-lincosamide-streptogramin group (Dutta and Devriese, 1982), which includes tylosin (Aarestrup and Cartensen, 1998).

Non-enteric bacteria: Antibiotic resistance is also quite common in non-enteric organisms such as

respiratory tract pathogens in all livestock species (Watts et al., 1994; Raemdonck et al., 1994), staphylococci from bovine mastitis (Brown and Scassera, 1990; Aarestrup and Jensen, 1998) and small animal infections (Blue and Wooley, 1977; Barsanti et al., 1985; Piriz et al., 1996).

Human health concerns

As indicated previously, the human health concern is the risk of direct transfer of resistant human pathogens or transfer via the food chain. In addition, antibiotic resistance genes may be transferred from animal pathogens or commensals to human pathogens. This topic has been the subject of recent reviews (van den Bogaard and Stobberingh, 1999, 2000; Barton, 2000). Salmonella and campylobacter are acknowledged food borne pathogens so it is logical to assume that antibiotic resistant strains of these organisms will also be transferred via the food chain. *E. coli* is an opportunist pathogen capable of infecting people via the food chain and causing enteric infections in young children and travellers as well as a range of other infections. Enteric infections with salmonella, *E. coli* or campylobacter rarely warrant antibiotic treatment and so one might argue that the problem is not nearly as important as MRSA or other major human resistance problems. However, treatment failure has been reported (Smith et al., 1999; Fey et al., 2000) and the livestock industries cannot ignore the problem. Enterococci have only been thought of as food borne organisms since the discovery of VRE in pigs and poultry and there is some dispute that this spread occurs from animals to people. However, there is evidence that transfer occurs (van den Bogaard and Stobberingh, 1999, 2000; Barton, 2000) and VRE can cause serious infections in severely ill hospitalised patients, further reducing the range of therapeutic options for those patients.

There are many reports of resistant bacteria in animals and of human isolates of the same organism with similar resistance patterns (Levy et al., 1976; Hunter et al., 1994; Nijsten et al., 1994, 1996; van den Bogaard et al., 1997; Fey et al., 2000). In addition, many published studies report the finding of the same resistance genes or resistant bacteria with the same genotype (van den Bogaard and Stobberingh, 1999, 2000). Reports on detection of resistant bacteria with the same resistance patterns and/or of the same genotype in food are also increasing (Klein et al., 1998; Manie et al., 1998; Quednau et al., 1998; Duffy et al., 1999; Butaye et al., 2000; Pavia et al., 2000) and more detailed systematic investigations are now under way (Kuhn et al., 2000).

Transfer of multi-resistant *S. Typhimurium* has been recognised as a serious problem for many years and studies in the UK particularly have demonstrated a

direct link between infected animals and people consuming milk or other products from such animals (Wall et al., 1995). *S. Typhimurium* DT104 is the current strain of major concern in the UK, Europe and North America. There is ample evidence for transfer of this organism via the food chain (Threlfall et al., 2000; Besser et al., 2000) or by direct contact (Fone and Barker, 1994).

Detection of apramycin resistance in human strains of *E. coli* or salmonella provides evidence of transfer of this type of resistance from animals to humans as apramycin is not used in human medicine (Wray et al., 1986). Hunter et al. (1993) reported the detection of apramycin resistance in *E. coli* isolates from a pig farmer and his pigs. Detailed investigations in Germany traced resistance to nourseothricin (a growth promotant antibiotic not related to any class of antibiotic used in human medicine) from pigs to pig farmers and their families and subsequently to residents of nearby towns and villages (Hummel et al., 1986). Clearly use in pigs was the source of resistance in this case.

Fluoroquinolone use in animals has also led to infections in people caused by resistant strains of campylobacter (Jacobs-Reitsma et al., 1994; Smith et al., 1999; Threlfall et al., 2000). A further concern with fluoroquinolone resistance is the emergence of resistance in salmonella or transfer of resistance from campylobacters to salmonella (Glynn et al., 1998). As a result of concerns about fluoroquinolone resistance the USA has indicated an intention to ban the use of fluoroquinolones in livestock, even for therapeutic purposes.

The first evidence for transfer of vancomycin resistance from enterococci in animals to human strains of enterococci came from observational studies (Danish Veterinary Laboratory, 1995; Aarestrup et al., 1996). However, the scientific evidence for the transfer of at least one type of vancomycin resistance, vanA resistance, is now compelling. Studies on the distribution of the vanA resistance determinant Tn1546 and genotyping studies on vanA *E. faecium* strains from animals, food and people point firmly in the direction of animals as the predominant amplifier if not the source of this resistance (Werner et al., 1997; Jensen et al., 1998a; Simonsen et al., 1998; van den Braak et al., 1998; Descheemaeker et al., 1999; Wegener et al., 1999). vanA *E. faecium* have also been found in various foods, primarily meats (van den Bogaard and Stobberingh 2000). However, vanB *E. faecium* (the predominant strain causing clinical problems in the USA) has not been isolated from animals (Woodford, 1998) and presumably emerged as a result of misuse and overuse of vancomycin in hospitals.

Recognition that animals were the source of vanA

VRE led to investigation of the resistance of animal strains of enterococci to other antibiotics under development for treatment of MRSA and VRE infections in people. For example, use of streptogramins in human medicine has been restricted because of the unavailability of a parenteral form. However, virginiamycin has been a useful growth promotant in animal husbandry for many years. In response to the increasing MRSA and VRE problems, and despite knowledge that virginiamycin was widely and legitimately used in animals, a semi-synthetic injectable human product quinupristin/dalfopristin was developed. When apparent cross-resistance between virginiamycin and dalfopristin-quinupristin was described (Danish Veterinary Laboratory 1998; Hammerum et al., 1998; Jensen et al., 1998b; Werner et al., 1998), there were calls for the banning the use of virginiamycin as a growth promotant in animals, to which the EU has responded. Continued registration of virginiamycin is under review in other countries, for example Australia.

Everminomycin, an orthosomycin, has just been withdrawn from clinical trials as a treatment for multiply-resistant Gram-positive organisms in people. It belongs to the same class of antibiotics as avilamycin which was specifically introduced into animal husbandry as there were no related human products at the time. Avilamycin-resistant enterococci are reported to have reduced sensitivity to everminomycin (Aarestrup, 1998) and avilamycin resistant enterococci are readily isolated from poultry treated with avilamycin but not from animals that have not been treated (Aarestrup et al., 2000a, b).

REDUCTION OF ANTIBIOTIC RESISTANCE

Reduction in antibiotic resistance problems in people could be assisted by improved on-farm disease control and new generation vaccines to reduce the prevalence of salmonellosis in livestock. Improvements in food production and food hygiene would reduce contamination of carcasses and meat with zoonotic food borne salmonella, campylobacter, *E. coli* and enterococci. However, there will be no specific reduction in antibiotic resistance in people until there is a concerted effort in hospitals, medical practices and the community to control the misuse and overuse of antibiotic in human medicine. There are sound reasons to also address antibiotic use in animals: on one hand resistance is an increasing problem in treatment and control of diseases in animals and on the other it is clear that resistant organisms and resistance genes can transfer from animals to people. One approach could be to adopt the "3Rs" approach from animal experimentation: reduction (of antibiotics); refinement (of antibiotic use); and replacement (of antibiotics).

Reduction of antibiotic use

Therapeutic and prophylactic use of antibiotics in animals could be improved by more accurate diagnosis of infectious disease. Where possible, samples should be submitted to diagnostic laboratories for determination of the cause of the disease. This would also enable assessment of antibiotic sensitivity and selection of the most appropriate therapy. In addition, it would provide clinical isolates for monitoring of antibiotic resistance - a key recommendation from many of the recent reviews. Where access to veterinary laboratories is not feasible, education of professional staff and training programs for para-veterinary workers and farmers should try to ensure such people have the well-developed clinical diagnostic skills. Handbooks setting out clinical signs and post-mortem examination findings for common infections should be provided.

Duration of treatment should be the minimum required to achieve recovery and antibiotics should be restricted to treatment and prevention of disease. That is, growth promotant compounds with antibacterial activity should be phased out as quickly as possible to preserve these drugs for treatment and prevention of infections.

All antibiotics should become prescription only medicines and not available over the counter to farmers or feed manufacturers. Only people with training in animal health should be able to prescribe treatment to try to ensure that antibiotic use is optimised. Restricting access to antibiotics will be difficult in countries with less well-developed animal health infrastructures. However, it is necessary to ensure antibiotics are used only when necessary, that the appropriate antibiotic is selected and appropriate advice is given on storage, administration, duration of treatment, withholding times (to minimise residues) and any supportive treatment required. Underpinning any program to reduce antibiotic use must be a comprehensive education program, some elements of which have already been mentioned. Farmers, animal health advisors and veterinary surgeons must all be aware of their responsibilities in use of antibiotics and there should be formularies and appropriate codes or guidelines in each country for prudent use of antibiotics.

Refining the use of antibiotics

Only animals that require treatment with antibiotics should be treated, rather than treating whole groups of animals simply because it is more convenient. On-farm Quality Assurance programs should include the goal of reducing antibiotic resistance - at the moment on-farm QA programs focus on reducing antibiotic residues and little attention is given to the resistance problem. Prophylactic medication should be refined by developing strategic interventions based on knowledge

of the epidemiology and pathogenesis of the diseases of concern. At present such medication often seems unplanned, with treatment triggered by an outbreak. Strategic planning may enable short sharp bursts of medication rather than use for extended periods of time. Narrow spectrum specific antibiotic therapy should be used as far as possible rather than broad-spectrum antibiotics. This will require more accurate and specific diagnosis of infections. Use of narrow spectrum antibiotics should reduce the resistance selection pressure on commensal and non-target bacteria. It may also assist if a system of rotation of antibiotic classes is introduced - however, some antibiotic resistance, for example tetracycline, persists for quite extended periods even in the absence of exposure to that antibiotic (Smith 1973; Hinton et al., 1984). Salyers and Amabile-Cuevas (1997) also point out that there is likely to be a rebound rapid re-emergence in resistance when an antibiotic is re-introduced after a period of non-use. A strategy first promoted in the Swann report (Swann, 1969) was to restrict growth promotant antibiotics to classes not used therapeutically in animals or people and unlikely to cross select for resistance to such compounds. This proposal should be extended where possible to restrict certain classes of antibiotics to human use (for example, fluoroquinolones and third generation cephalosporins). This may be easier to do if and when new classes are developed. If there is a need to use these antibiotics for treatment of individual animals, then it should be on the basis of a special permit.

Replacement of antibiotics

Many approaches for replacement of antibiotics are already available. Improvements in hygiene and herd/flock management can significantly reduce the need for antibiotics. In the last 20 years many effective vaccines have been developed and application of biotechnology promises new generation for vaccines for many conditions where conventional vaccines have not been effective or have been unattainable. Specific pathogen free (SPF) flocks also have much to offer, particularly where hygiene, management and disease control strategies allow preservation of the disease free status. Other techniques under investigation include dietary manipulation, competitive exclusion and probiotics to control and prevent enteric diseases. Bacteriophages may also have a role to play.

CONCLUSIONS

It is critical for the quality of human and animal life to reduce the extent of antibiotic resistance in human and animal pathogenic and commensal bacteria. This necessitates reduction and refinement of antibiotic use and replacement of antibiotics where possible. It is

difficult to justify use of compounds with antibacterial activity as growth promotants and these compounds must be reserved for treatment of infectious diseases. Medical authorities need to take action to reduce misuse and overuse of antibiotics in hospitals and the community generally and it would be advantageous to protect critical human antibiotics by not using them in veterinary practice.

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