

DEVELOPMENT OF ANTIBIOTIC RESISTANCE IN LIVESTOCK PRODUCTION

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INTRODUCTION

The use of antimicrobial products has remained an integral part of livestock production since the discovery of their benefits in the early 1950s. Estimates vary widely with regard to the relative amounts of antimicrobials used in agriculture compared to use for human therapies, however, it is most commonly reported that at least half of such products used in the US are directed towards livestock (Lee et al., 1993; Table 1). The two primary uses of antibiotics for meat animal production include treatment or prevention of diseases (therapeutic) and enhancement of production performance (nontherapeutic). Antibiotics when used therapeutically are generally applied after the onset of a disease condition and are used under the direction of a veterinarian. Nontherapeutic use of antimicrobials includes low doses (typically less than 200 g/ton of feed) over longer periods of time (NRC, 1999), most often applied through inclusion in feedstuffs. The use of feed-based antimicrobials has consistently been shown to benefit livestock production, increasing the ability of farms to maintain profitable margins (Stahly et al., 1980; Cromwell et al., 1996), reducing effects of animal wastes on the environment (Roth and Kirchgessner, 1993), and lowering animal pathogen, and in some cases foodborne pathogen carriage in livestock (Kyriakis et al., 1996; Ebner and Mathew, 2000). These benefits have helped in the development of modern animal production practices, allowing producers to maintain profitable margins with less labor and capital (Hurt et al., 1992), while at the same time meeting ever increasing consumer demands for a safe, high quality, and relatively inexpensive protein source.

RISKS ASSOCIATED WITH ANTIMICROBIAL USE

While the discovery of antimicrobial agents has been of paramount importance to human medicine and has provided significant benefits to agriculture, the use of these compounds across both aspects has been linked to the emergence and/or increased prevalence of antibiotic resistant bacteria (Novick, 1981; Gomez-Lus, 1998). Much of the above concern centers around the persistence of antibiotic resistant bacteria in livestock and potential impact on human therapies (Wray et al., 1986; Hunter et al., 1993; Berends et al., 2001). As zoonotic bacteria, such as *Salmonella* and *Campylobacter*, are frequently associated with meat products, it has been implied that antibiotic resistant strains of these as well as other contaminating bacteria, could pose a significant health hazard if contracted by consumers. Additionally, non-pathogenic opportunistic bacteria, such as *E. coli* and enterococci, have the ability to transfer resistance genes to pathogenic bacteria and thus are also of concern (Berends et al., 2001). Such concerns have been expressed for many years, with the convening of international committees, such as the Northrope and Swann committees, convening as early as the 1960s, to address this issue (NRC, 1999). Research focusing on antibiotic resistant bacteria in livestock has also been conducted for some time, and some results have been proposed to link agricultural use of antimicrobials with

resistant bacteria of relevance to human health. Holmberg et al. (1984), for example, noted that food animals were the source of 69% of resistant salmonella infections in humans and 46% of

Table 1. Partial list of antibacterials approved for cattle, poultry and swine

Drug	Antibiotic Family	Used in Feed	Used in Human Medicine
Amoxicillin	β -lactam	no	yes
Ampicillin	β -lactam	no	yes
Apramycin	aminoglycoside	yes	no
Arsanilic acid	arsenical	yes	no
Bacitracin	bacitracin	yes	yes
Bambermycin	bambermycin	yes	no
Carbadox	quinoxaline	yes	no
Ceftiofur	cephalosporin	no	no
Chloramphenicol	chloramphenicol	no	yes
Chlortetracycline	tetracycline	yes	yes
Dihydrostreptomycin	aminoglycoside	no	yes
Erythromycin	macrolide	yes	yes
Enrofloxacin	quinolone	no	no
Florfenicol	chloramphenicol	no	yes
Gentamicin	aminoglycoside	no	yes
Hygromycin	aminoglycoside	yes	no
Lincomycin	lincosamide	yes	yes
Neomycin	aminoglycoside	yes	yes
Novobiocin	dibasic acid	yes	yes
Oxytetracycline	tetracycline	yes	yes
Penicillin	β -lactam	yes	yes
Pirlimycin	lincosamide	no	no
Roxarsone	arsenical	yes	no
Spectinomycin	aminoglycoside	no	yes
Streptomycin	aminoglycoside	no	yes
Sulfaethoxyypyridazine	sulfonamide	yes	no
Sulfamerazine	sulfonamide	yes	no
Sulfamethazine	sulfonamide	yes	no
Sulfamethoxine	sulfonamide	yes	no
Sulfaquinoxaline	sulfonamide	yes	no
Sulfathiazole	sulfonamide	yes	no
Tetracycline	tetracycline	no	yes
Tiamulin	diterpene	yes	no
Tilmicosin	macrolide	yes	no
Tylosin	macrolide	yes	no
Virginiamycin	streptogramin	yes	no

(Adapted from Ebner, 2002)

susceptible salmonella outbreaks. A later study conducted by Hunter et al. (1993) noted that gentamicin-resistant *E. coli* isolated from humans were also resistant to apramycin. While both drugs belong to the aminoglycoside family, gentamicin is used for both animal and human therapies whereas apramycin is used exclusively in animals. In that study, the proportion of gentamicin-resistant isolates, which were also resistant to apramycin, increased from 16% in 1981-5 to 40% in 1986-90.

Another study focused on the presence of apramycin-resistant *E. coli* association with a stockman working on a pig farm (Hunter et al., 1994). Apramycin-resistant *E. coli* isolated from both the stockman and pigs contained similar plasmid profiles and identical antibiotic resistance patterns, suggesting that the stockman may have acquired apramycin-resistant *E. coli* through direct contact with pigs. The National Antimicrobial Resistance Monitoring System (NARMS), which was established through the cooperative efforts of the Centers for Disease Control (CDC), the USDA, and the Food and Drug Administration, to monitor long-term changes in prevalence of resistant bacteria in human and animal isolates, has also provided evidence that the numbers of resistant bacteria are increasing.

Research conducted by our group has shown that use of antimicrobials in livestock production does promote populations of resistant bacteria in the GI tract of those animals (Ebner and Mathew, 2000; Mathew et al., 2001a; Mathew, 2001b). However, it has been much more difficult to assess the risks such bacteria pose to humans. As bacterial foodborne illness is seldom treated with antibiotics, risk assessments often conclude that the impact of resistant bacteria associated with livestock is of negligible importance to human health (Hurd et al., 2003; Doores et al., 2003). Thus the primary concerns remain those associated with resistant organisms causing nosocomial infections, including methicillin-resistant *Staphylococcus aureus*, vancomycin resistant enterococcus (VRE), and other bacterial agents associated with blood borne infections. Resistance in these strains appears to have originated primarily through extensive use of antimicrobials in human medicine. Still, there remains concern that the global increase in resistant bacteria is in part due to the widespread use of antimicrobials in agricultural settings, and thus considerable research continues to address ways to reduce the use of antimicrobials and/or limit the promotion of antimicrobial resistant bacteria in food animals.

Some findings suggest that factors other than antibiotic exposure may contribute to a high prevalence and pervasiveness of antibiotic-resistant bacteria found in livestock (Langlois, 1988; Cullen et al., 2001). Langlois et al. (1988) studied the effect of age and housing on antibiotic resistance, noting the proportion of resistant bacteria was generally higher in pigs 6 months of age or less. Housing also had an effect, as pigs from sows raised on pastures exhibited the lowest number of resistant isolates, whereas bacteria from pigs housed in the farrowing house or finishing unit expressed a higher prevalence of resistance. Another study by Mathew et al. (2001b) indicated that weaning in pigs resulted in a significant increase in bacterial resistance to antimicrobials, even in the absence of the use of these products. However, in that same study, animals exposed to antimicrobials were shown to harbor *E. coli* with a significantly higher level of resistance, and persistence of these organisms was increased in pigs with such exposure. It has been further observed that persistence of resistant bacteria is highly antibiotic dependent, as resistance to the aminoglycosides appears to subside following use (Mathew et al., 1998; Mathew et al., 2001a), whereas tetracycline resistance persisted and generally increased up to the

time that pigs went to slaughter (Mathew 1998). Tetracycline resistance has been shown by others to persist for many years following exclusion of that antimicrobial from the farm (Langlois et al., 1983).

We have shown that duration and type of dose of some non-therapeutic antibiotics can have a significant effect on resistance levels in *E. coli* in pigs (Mathew et al., 2001a). In that work, we observed that antimicrobial rotations consisting of compounds of the same family (aminoglycosides: apramycin, gentamicin, neomycin) greatly increased the minimum inhibitory concentrations (MIC) of apramycin required to inhibit growth of *E. coli* obtained from pigs, compared to controls which did not receive antibiotics and compared to isolates from pigs receiving an antibiotic rotation consisting of unrelated antimicrobials (apramycin, carbadox, sulfamethazine). Additionally, feeding pulse doses of apramycin (inclusion for 3 days, exclusion for 3 days and then repeating for the remainder of a 14-day period, greatly reduced resistance in *E. coli* compared to other antimicrobial inclusion regimens (Table 2).

Table 2. Effects of 14-day antibiotic dosing regimens on sensitivity to apramycin by *E. coli* recovered from pigs¹.

Antibiotic dosing regimen ²	Day Post Challenge					
	3	6	10	13	17	31
Control	4.3	3.9	3.5	3.1	2.3	2.6
Rotation S	3.5	4.2	200.5*	182.3*	140.9*	7.6*
Rotation D	2.6	38.8*	44.1*	13.8*	14.0*	3.8
Gradient	3.5	3.5	3.5	68.5*	109.9*	2.8
Pulse	5.2	4.3	3.6	4.0	7.0*	3.7
Label	5.9	41.1*	55.5*	49.0*	49.5*	6.6*

¹ Data are Least Squares Means of minimum inhibitory concentrations (MIC) in micrograms per milliliter, with 64 isolates for each mean.

² Control, = no antibiotic treatment; Rotation S = rotation with similar antibiotics (apramycin, 150 g/ton of feed; neomycin, 22 mg/kg in drinking water; gentamicin 6.6 mg/L of drinking water); Rotation D = rotation with dissimilar antibiotics (apramycin, 150 g/ton of feed; sodium sulfamethazine, 118 mg/kg in drinking water; carbadox 50 g/ton of feed); Gradient = increasing initial apramycin dose (50 g/ton of feed) by 50 g/ton increments at 5-day intervals; Pulse = pulse dosing with apramycin at 150 g/ton of feed at 3-day intervals; Label = maximum label dose of apramycin, 150 g/ton of feed.

*Indicates difference from control within day at $P < .05$.

(Adapted from Mathew et al., 2001a)

Further work in our lab showed that animal stressors, including cold, heat, and crowding, can result in increased numbers of resistant bacteria and/or persistence of such bacteria in swine (Arnett et al., 2003; Table 3). In that report, we suggested that stress might promote physiological changes, which may then alter the gut environment, promoting colonization by resistant bacteria and/or an increased transfer or expression of genetic resistance in intestinal bacteria. Garner and Mathew (2002) also observed increased resistance in bacteria of pigs born

to sows which had earlier exposure to antibiotics, thus indicating effects of antimicrobial use on bacterial resistance across generations of animals.

Table 3. Effects of animal stressors on sensitivity to apramycin by *E. coli* isolated from pigs¹

Treatment ²	Days Post Challenge							
	0	2	7	14	28	64	148	149
Control-1	2.3	2.8	1.3	1.2	1.0	1.2	1.0	1.3
Control-2	3.0	1.5	1.3	245.1*	1.3	1.2	1.8	1.6
Cold stress	4.8	1.7	17.3*	224.8*	76.8*	15.5*	1.1	1.4
Heat stress	2.4	2.1	1.5	101.6*	4.1	3.5	1.1	1.9
Crowding	2.0	2.5	1.2	25.4*	10.0*	11.6*	1.2	1.6
Low sanit	3.6	4.0	5.7	194.0*	4.9	2.2	1.5	1.4
Oxytet	3.2	4.4	1.9	90.5*	5.0*	8.5*	1.1	1.4
Interming	2.2	1.8	1.8	138.2*	11.3*	2.6	1.3	1.4

¹Data are Least Squares Means of minimum inhibitory concentrations (MIC) in micrograms per milliliter with 32 isolates per mean.

²Control-1 = optimal conditions, no apramycin, Control-2 = optimal conditions and apramycin exposure (150 g/ton of feed), Cold stress = room maintained at 6°C below optimal temperature, Heat stress = room maintained at 6°C above optimal temperature, Crowding = Overcrowding, Low sanit = Poor Sanitation, Oxytet = Treatment with oxytetracycline, Interming = intermingled pigs (exposed and not exposed to apramycin).

*Treatments differ from Control-1 within day (P < .05).

(From Arnett et al., 2003)

MECHANISMS OF RESISTANCE

The mechanisms that define antibiotic actions are diverse and involve a variety of bacterial functions and structures. Likewise, resistance mechanisms and the ability of bacteria to maintain those mechanisms in the absence of antimicrobial use also varies considerably. Thus, prevalence, level of resistance and persistence of such on the farm varies considerably between the various antimicrobials. Antimicrobials usually operate by inhibiting important functions of the bacterial cell for survival or replication (Bryan, 1982). For example, tetracyclines, which are broad-spectrum agents, exhibiting activity against a wide range of gram-positive and gram-negative bacteria, act by preventing both enzymatic and non-enzymatic binding of aminoacyl-tRNA to the ribosome, thereby inhibiting protein synthesis. This is achieved through the action of a *tet* molecule, which binds strongly to the 70s unit of the ribosome. Weak binding also occurs at the 30s subunit, further preventing essential aminoacyl-tRNA binding (Bryan, 1982).

The primary mechanism of tetracycline resistance is through alteration of the ribosome structure, thus preventing the binding of tetracycline (Salyers et al., 1990). Efflux genes associated with some gram-negative bacteria are widely distributed and are usually associated with large transferable plasmids (self replicating, non-chromosomal DNA elements). Bacteria also confer resistance to tetracyclines through ribosomal protection proteins (Taylor and Chau, 1996). These

proteins protect the ribosomes from the action of tetracyclines and confer a wider spectrum of resistance to tetracyclines. The large number and widespread existence of plasmid and chromosomal genes associated with tetracycline resistance, and the ease in which these mechanisms can be maintained in the absence of tetracycline exposure have resulted in a highly prevalent and persistent tetracycline resistant bacterial population in livestock.

Aminoglycosides are another class of antimicrobials that act through the inhibition of protein synthesis (Mortensen et al., 1996). Aminoglycosides create a firm bond with the structural component of the 30s ribosomal subunit to inhibit protein synthesis. The bonding of aminoglycosides is much stronger than that of other protein synthesis inhibitors, possibly accounting for the bactericidal (killing) rather than bacteriostatic (inhibition of growth) action of this family of antimicrobials. Three primary mechanisms are associated with resistance to aminoglycosides. These include decreased transport across the cell membrane, preventing access to the ribosomes, ribosomal modification preventing antibiotic binding, and expression of aminoglycoside-modifying enzymes. In the case of aminoglycoside resistance, modification of the ribosomal target does not appear to be mediated by plasmid genes. Rather, a mutation in the ribosomal protein may cause a decreased affinity for the drug. However, the primary mechanism of resistance to aminoglycosides is through the production of modifying enzymes encoded by genes, which often exist on transferable genetic elements known as transposons. Resistance results in this case through production of a single enzyme coded by the AAC(3)-IV gene. This enzyme is also capable of modifying gentamicin and tobramycin, which are important aminoglycosides used in human medicine.

Beta lactam antimicrobials, including penicillin-like compounds and cephalosporins, disrupt cell wall formation at the peptidoglycan layer; thus these compounds have primary use against Gram positive bacteria (Prescott et al., 2000). The majority of beta-lactam resistant bacteria produce enzymes known as beta lactamases that alter the drug's affinity for the target by degrading a portion of the beta-lactam ring of the drug. As with tetracycline resistance, the genes for beta lactam resistance are widespread and easily maintained in some bacteria, thus resistance to this class of antimicrobials is common among bacterial populations.

Sulfonamides are a class of antimicrobials used extensively in animal and human medicine. These antimicrobials inhibit tetrahydrofolic acid (THF). Bacterial cells, like mammalian cells, require a constant replenishing of THF for the synthesis of nucleic acids and certain amino acids. Such folic acid antagonists are able to disrupt this pathway by irreversibly binding to either dihydrofolate synthase or dihydrofolate reductase, two enzymes necessary in the production of THF. Blocking THF synthesis prevents production of nucleic acid precursors thereby preventing DNA replication (Prescott et al., 2000). Sulfonamide resistance generally involves an efflux mechanism that prevents these antimicrobials from accumulating in the bacterial cell. However, in some cases altered THF reductases have also been described in sulfonamide resistant bacteria.

Quinolones and fluoroquinolones, which include carbadox, and enrofloxacin respectively, act by irreversibly binding to DNA gyrase and DNA topoisomerase, which are essential for DNA replication, thereby inhibiting reproduction of bacteria (Prescott et al., 2000). Resistance to these drugs is accomplished through mutation of the genes coding for these two enzymes, thus structurally altering the target of these antimicrobials. As this resistance mechanism involves

mutations at the chromosomal level rather than through transferable genes (plasmid or transposon mediated), resistance to quinolones and fluoroquinolones is currently less widespread than resistance to other families of drugs. However, concerns are being raised that frequent and long term use of this class of drugs could eventually lead to transferable resistance elements which could then more rapidly disseminate through bacterial populations.

TRANSFER OF ANTIMICROBIAL RESISTANCE GENES

Transfer of resistance genes between similar and non-similar bacteria can occur through several mechanisms. Genes can be transferred vertically, that is, passed down through generations of bacteria, creating clonal resistant types, or resistance genes can be passed horizontally, to initially sensitive bacteria of similar or non-similar species. The occurrence and rate of transfer are dependent upon the location of the gene (plasmid versus chromosome), the number and size of the genes required for a specific resistance, and linkages with transferable gene elements. As a result, prevalence and persistence of genetic resistance differs depending upon the type of antibiotic affected by the resistance. Three primary mechanisms of bacterial gene transfer are described below and depicted in Figure 1.

Transduction

Resistant phenotypes can be transferred from one bacterial cell to another through bacteriophages, which are viruses that infect bacteria. In this process the phage infects the bacterium and integrates into the bacterial chromosome. At a later stage the phage extracts itself from the bacterial genome, however this process is not always exact and bacterial genes can sometimes become packaged into the exiting virus particle. When the phage infects another cell and integrates into the bacterial chromosome, those bacterial genes can become integrated into the recipient host's genome (Ochman et al., 2000). The role of transduction in bacterial genome evolution is quite large. It is estimated that through this process, nearly 18% of the *E. coli* genome is composed of foreign genes (Ochman et al., 2000).

Transformation

Resistance can also be transferred horizontally from cell to cell through transformation. In this process, free DNA existing outside of the bacterium is transferred into the cell. Through a recombination process, the DNA is incorporated into the host genome (McClane and Mietzner, 1999). While transformation is easily demonstrated in the laboratory, it is unlikely that many resistant bacteria are generated through this mechanism.

Conjugation

While resistance acquisition through transduction and transformation should not be ignored, it is generally thought that most antibiotic resistance genes are exchanged through plasmid conjugation (Anderson, 1968; Toussaint and Merlin, 2002). Most plasmids associated with antibiotic resistance are conjugative, meaning that they possess the machinery to transfer copies of themselves to adjoining, often times unrelated, bacterial cells. The process of plasmid conjugation is quite elegant. Through a set of genes encoded on the plasmid itself, a protein

pilus (sex pilus) is formed connecting the donor cell (male) with the recipient (female) through a conjugal tube. In the replication process, a copy of the plasmid is passed through the pilus as single-stranded DNA. Once inside the recipient cell, the plasmid is replicated using the host machinery into functional, double stranded DNA (Willots, 1985).

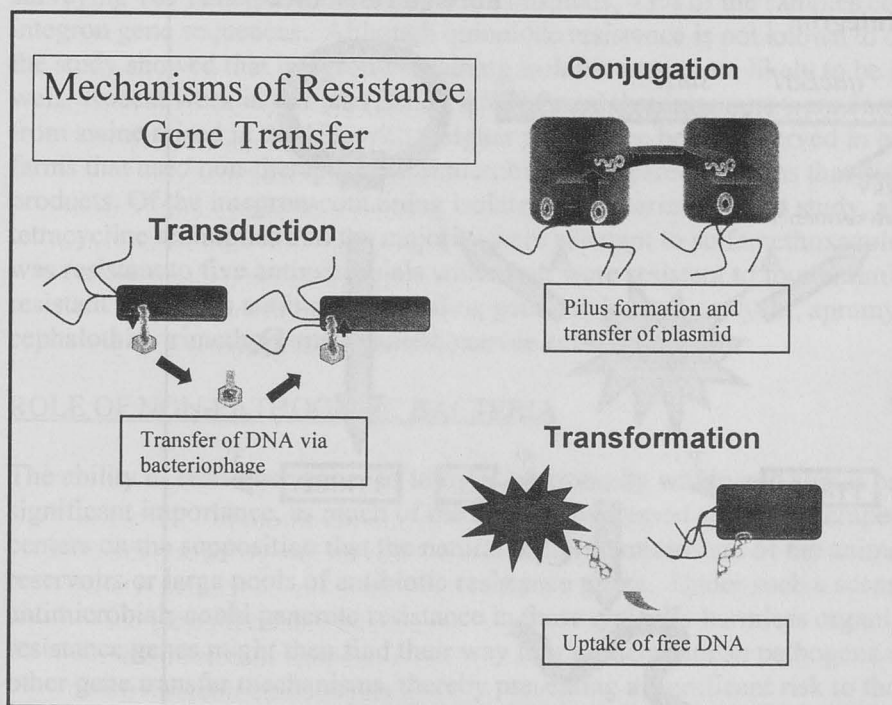


Figure 1. Depiction of primary resistance gene transfer mechanisms in bacteria

INTEGRONS

In recent years, many different and diverse genes responsible for antimicrobial resistance have been found in genetic units known as integrons (Stokes and Hall, 1991; Sunde and Sorum, 1999) (Figure 2). Integrons allow a bacterium to capture foreign antibiotic resistance “cassettes” which may carry multiple genes for resistance to a wide range of antimicrobials. Integrons are also often associated with transferable genes, including “transposons”, which have the ability to self-transfer and insert themselves into genomes of many types of bacteria. As such, some integrons can move readily through bacterial populations, promoting a stable resistance to several unrelated antibiotics simultaneously. The characteristic five-way resistance (resistant to chloramphenicol, sulfonamide, tetracycline, ampicillin, and streptomycin) of *Salmonella enterica* Typhimurium DT104 results from that strain’s possession of an integron. Integrons present a greater level of risk with regard to promotion of antibiotic resistance in agricultural and human environments, as they provide a ready-made vehicle for a rapid incorporation and spread of resistance genes, including those bestowing resistance to newer antibiotics as they may come into use. Additionally, integrons present the risk that the use of a single antibiotic, such as

tetracycline, could select for an integron-carrying bacterial strain, bringing with it the simultaneous resistance to several unrelated antimicrobials.

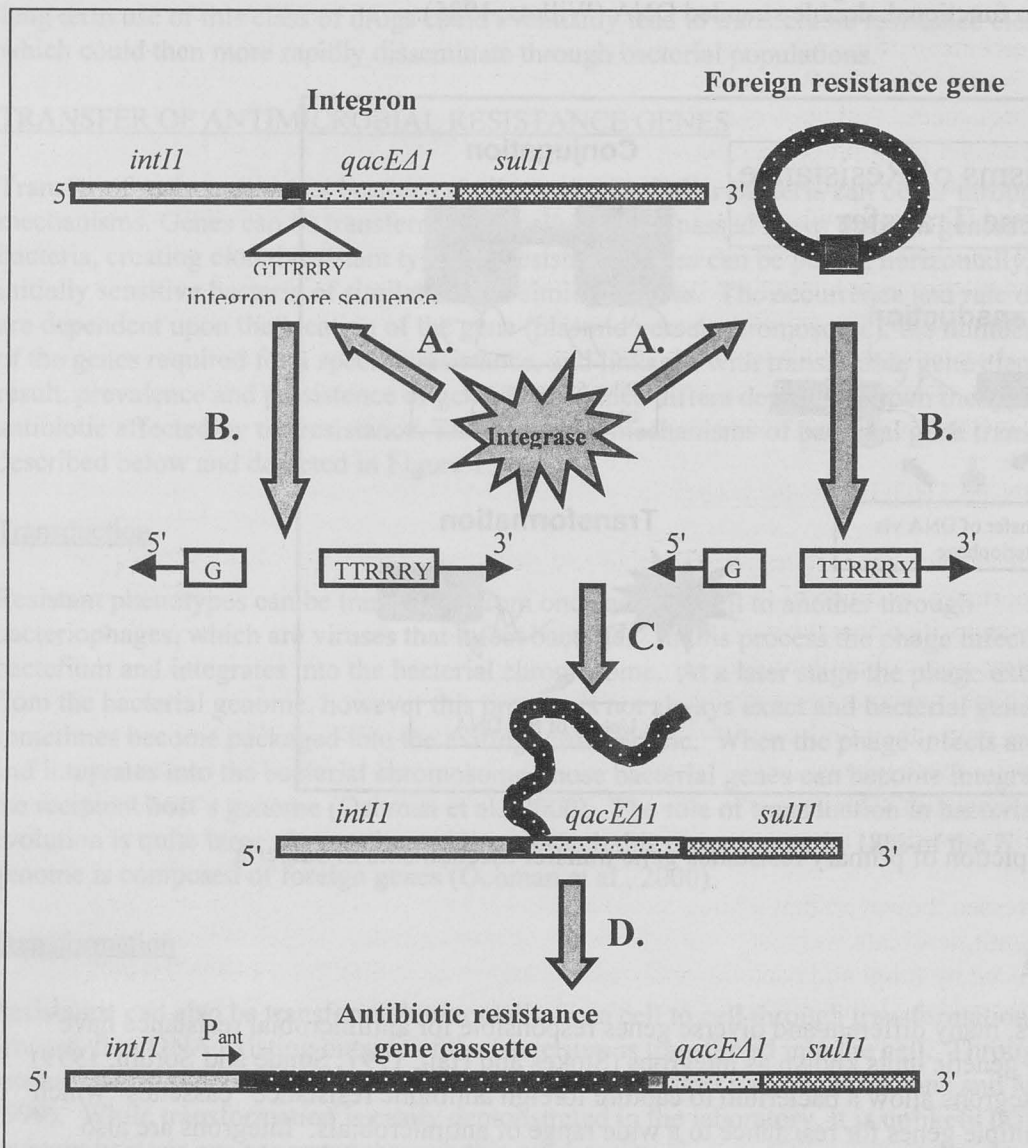


Figure 2. Depiction of exogenous resistance gene incorporation into Class I integron. *IntI1* = integrase gene, *qacEΔ1* = gene coding for resistance to quaternary ammonia compounds, *sulI1* = gene coding for resistance to sulfonamides. Additional resistance genes are incorporated into the region downstream of the promoter region (P_{ant}). (From Ebner, 2002)

A number of studies examining integron-mediated antibiotic resistance have been conducted by agricultural scientists, many in response to earlier concerns over the rapid dissemination of *Salmonella enterica* serovar Typhimurium DT104 (Glynn et al., 1998; Poppe et al., 1998; Humphrey, 2001). In an examination of multidrug-resistant *E. coli* isolated from swine, Sunde

and Sorem (1999) reported that of 134 multi-resistant isolates, 17 were found to carry class I integron gene sequences. In each case the integrons contained streptomycin resistance cassettes. In eight cases, the integrons were carried on plasmids and the resistant phenotypes could be transferred to susceptible strains by conjugation. Martinez-Freijo et al. (1998) however, found a much higher percentage of integron-positive, clinically important gram-negative bacteria. In surveying 163 isolates from 14 European hospitals, 43% of the samples contained class I integron gene sequences. Although quinolone resistance is not known to be integron-mediated, the study showed that integron-containing isolates were more likely to be resistant to that drug as well. Recent work in our lab (Ebner, 2002) found that integrons were common in *E. coli* isolated from swine raised in the US, with a higher prevalence being observed in bacteria coming from farms that used non-therapeutic antimicrobials, compared to farms that did not use such products. Of the integron-containing isolates characterized in that study, all were resistant to tetracycline antibiotics and the majority were resistant to sulfamethoxazole as well. One isolate was resistant to five antimicrobials while four were resistant to four antimicrobials. Several were resistant to various antibiotics including gentamicin, streptomycin, apramycin, ampicillin, cephalothin, trimethoprim/sulfamethoxazole and kanamycin.

ROLE OF NON-PATHOGENIC BACTERIA

The ability of resistance genes to transfer horizontally within and across bacterial species is of significant importance, as much of the concern expressed over nontherapeutic antimicrobial use centers on the supposition that the natural bacterial microflora of the animal gut could act as reservoirs or large pools of antibiotic resistance genes. Under such a scenario, persistent use of antimicrobials could generate resistance in these typically harmless organisms and these resistance genes might then find their way into virulent human pathogens via conjugation or other gene transfer mechanisms, thereby presenting a significant risk to the human population. While clear evidence for such has yet to be presented outside of the laboratory, it remains a challenge for those working in agriculture to counter such claims.

It should be stressed, however, that antibiotic resistance would exist in nature even without human use of antimicrobials, as most antimicrobial compounds are derivatives of products naturally produced by fungi and bacteria, and such organisms must themselves have the genetic capacity to withstand the lethal effects of their own products. Likewise, other organisms, which can find an advantage by resisting natural antimicrobial products, will eventually acquire such genes and the ability to transfer them to their offspring. Thus it is common to find a small percentage of bacteria carrying genes for antibiotic resistance, even without previous exposure to antimicrobials. The concern, rather, is whether the more powerful selection pressure resulting from human use of antibiotics serves to increase the level of antibiotic resistance in nature, and if so, how much risk does this present to the human population.

FINDING NON-ANTIBIOTIC ALTERNATIVES

In response to the above concerns, considerable work has been underway to find alternatives to antibiotics in agriculture, and in particular to decrease our dependence on feed-based nontherapeutic antibiotics, which appear to present the greatest risk for antibiotic resistance. A number of compounds have been proposed to provide performance benefits when included in

swine diets. These include organic acids, modifiers of the gut bacteria, and immune enhancers. As of yet, however, none of these alternatives have been proven to consistently match the cost effectiveness, convenience, and performance benefits currently offered by antimicrobials. It is important however, that as we evaluate alternatives, we maintain an appropriate perspective and properly define expectations so that we can identify those products that offer at least partial benefits as those currently provided by nontherapeutic antibiotics. It is not likely, for example, that alternative feed-based growth promoters will be able to overcome serious management or health problems that have in the past been managed through therapeutic antibiotics. However, even subtherapeutic antibiotics would not be expected to perform at this level. Producers should also understand that the ability of antibiotics to enhance performance is directly related to the level of animal management and husbandry, with benefits of antimicrobials being more pronounced when sub-optimal conditions or poor management occur (Cromwell, 2001). Thus the first step in reducing reliance on growth promoting antibiotics should be to optimize management, particularly during critical growth periods and times of stress.

We need to also recognize that the growth promoting mechanisms of antibiotics may differ considerably from those of proposed alternatives. This in turn will likely affect how well alternatives can match the performance benefits of antibiotics. For example, some evidence indicates that subtherapeutic antibiotics work in part by decreasing the microbial load in the gut, resulting in a reduction in intestinal cell turnover and reducing energy use by the intestinal tissues. Because the intestinal tissues consume a disproportionately large amount of energy, the savings to the animal can be significant. This results in additional nutritional resources going to production parameters. In contrast, most alternative compounds studied thus far have not been found to reduce microbial loads in the gut and thus they will not likely mimic a primary mechanism of growth promoting antibiotics. Instead, alternative compounds may alter the *proportions* of specific gut bacterial species, limiting numbers of unfavorable bacteria while promoting the colonization of more favorable species. Thus performance effects of alternative compounds may be subtler than those of antibiotics. Additionally, because our knowledge of the interactions between the intestinal bacteria, nutrients, and animal host is currently incomplete, progress to identify appropriate alternatives or to increase the effectiveness of current alternatives has been limited.

CONCLUSION

It remains to be seen how great of an impact recent concerns over antibiotic resistance will have on use of antimicrobials in US livestock production. Those concerns and any subsequent regulations may reduce our access to antimicrobial products, particularly for growth promoting purposes. It is likely that newer antibiotics will face greater scrutiny and more difficulty in approval for nontherapeutic use. While increased restrictions may present some difficulties for producers who have relied heavily on antimicrobials in their production systems, it is not likely that high production levels will become impossible without growth promoting antimicrobials. Producers who are willing to utilize a variety of dietary strategies and who can maintain optimal husbandry conditions will likely have the greatest ability to make the transition away from extensive use of growth promoting antimicrobials, at least in some stages of production. The ultimate goal should be to provide consumers with a product that they widely accept as being nutritious and healthful. As a result, producers will find that the market share for agricultural products will be increased, leading to more profitable enterprises.

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