

Antimicrobial Growth Promoters Used in Animal Feed: Effects of Less Well Known Antibiotics on Gram-Positive Bacteria

Patrick Butaye,* Luc A. Devriese, and Freddy Haesebrouck

Laboratory of Veterinary Bacteriology and Mycology, Department of Pathology, Bacteriology and Poultry Diseases,
Faculty of Veterinary Medicine, University of Ghent, 9820 Merelbeke, Belgium

INTRODUCTION	175
DIFFERENTIATING SUSCEPTIBILITY AND RESISTANCE TO GROWTH-PROMOTING	
ANTIBIOTICS	176
Bambermycin	177
The product	177
Mechanism of action	177
Spectrum of activity.....	177
Prevalence of resistance.....	177
Pharmacokinetics and toxicity	177
Effects on intestinal flora.....	178
Streptogramins	178
The products.....	178
Activity.....	178
Resistance genes and mechanisms.....	178
Prevalence of resistance.....	179
Pharmacokinetics.....	180
Effects on intestinal flora.....	180
Avilamycin	180
The product	180
Activity.....	180
Resistance	180
Pharmacokinetics.....	180
Effects on intestinal flora.....	180
Bacitracin	181
The product	181
Activity.....	181
Resistance mechanisms.....	181
Prevalence of resistance.....	181
Pharmacokinetics and toxicity	181
Effects on intestinal flora.....	181
Ionophore Antibiotics	181
The products.....	181
Mechanism of action	182
Resistance	182
Pharmacokinetics and toxicity	182
Effects on intestinal flora.....	183
Other Growth-Promoting Antibacterials	183
Quinoxalines.....	183
Efrotomycin.....	183
CONCLUDING REMARKS	183
REFERENCES	183

INTRODUCTION

Shortly after the introduction of the therapeutic use of antibiotics, the growth-promoting effect of these products in chickens was discovered by feeding fermentation offal from the chlortetracycline production of *Streptomyces aureofaciens*

(122). Several antibiotics have been in use as growth promoters of farm animals ever since. The introduction of these agents coincided with intensive animal rearing. These products improved feed conversion and animal growth and reduced morbidity and mortality due to clinical and subclinical diseases. The average growth improvement was estimated to be between 4 and 8%, and feed utilization was improved by 2 to 5% (90).

The mechanisms of growth promotion are still not exactly known. Experiments with germ-free chickens have seemed to indicate that the action of the growth promoters is mediated by

* Corresponding author. Present address: VAR-CODA-CERVA, Groeselenberg 99, B1180 Brussels, Belgium. Phone: 32 (0)2 379 04 15. Fax: 32 (0)2 379 06 70. E-mail: pabut@var.fgov.be.

TABLE 1. Growth-promoting antibiotics allowed for use in the EC, both past and present

Antibiotic	Banned since:	Antibiotic group	Related therapeutics	Mechanism of action
Bamermycin		Glycolipid		Inhibition of cell wall synthesis
Bacitracin	1999	Cyclic peptide	Bacitracin	Inhibition of cell wall synthesis
Monensin		Ionophore		Disintegration of cell membrane
Salinomycin		Ionophore		Disintegration of cell membrane
Virginiamycin	1999	Streptogramin	Quinupristin/dalfopristin	Inhibition of protein synthesis
Tylosin	1999	Macrolide	Erythromycin and others	Inhibition of protein synthesis
Spiramycin	1999	Macrolide	Erythromycin and others	Inhibition of protein synthesis
Avilamycin		Orthosomycin	Everninomycin	Inhibition of protein synthesis
Avoparcin	1997	Glycopeptide	Vancomycin, teicoplanin	Inhibition of cell wall synthesis
Ardacin	1997	Glycopeptide	Vancomycin, teicoplanin	Inhibition of cell wall synthesis
Efrotomycin		Elfamycin		Inhibition of protein synthesis
Olaquinox	1999	Quinoxaline		Inhibition of DNA synthesis
Carbadox	1999	Quinoxaline		Inhibition of DNA synthesis

their antibacterial effect (91). Four hypotheses have been proposed to explain their action: (i) nutrients may be protected against bacterial destruction; (ii) absorption of nutrients may improve because of a thinning of the small intestinal barrier; (iii) the antibiotics may decrease the production of toxins by intestinal bacteria; and (iv) there may be a reduction in the incidence of subclinical intestinal infections (91).

The use of antibiotics as feed additives has been a hallmark of modern animal husbandry, but this widespread practice is not without criticism. In the early years, all antibiotics were allowed for use, although some did not enhance growth and many were too expensive. The first discussions on the use of antibiotics as growth promoters began in the late 1960s and resulted in the "Swann Report," which was issued in the United Kingdom (20). Concerns were raised that the use of antibiotics as therapeutics and for growth promotion could lead to a problem of increasing resistance in bacteria of human and animal origin, particularly regarding resistance in gram-negative bacteria (*Salmonella* spp. and *Escherichia coli*). In the United Kingdom, the Swann Report proposed that antibiotic use for growth promotion should be restricted to antibiotics that (i) make a significant economic difference in the raising of livestock, (ii) have little or no application as therapeutic agents in humans or animals, and (iii) do not impair the efficacy of a prescribed therapeutic drug through the development of resistant strains. It was suggested that antibiotic residues in meat would not impair human health. Specifically, it was recommended that the use of penicillins, tetracyclines, tylosin, and sulfonamides as growth promoters be discontinued. This report also formed the basis for the European legislation in Directive 70/524, in which a list was published of allowable additives with their maximum and minimum dosages, withdrawal period from slaughter, and animal species in which the product may be used. To be included in the list, additives should meet the following conditions: (i) they must have a favorable effect on livestock production; (ii) they should not endanger animal or human health; (iii) their nature and level must be controllable; (iv) the levels included should not reach those intended for treating or preventing animal disease; and (v) they should not be in use for medical or veterinary purposes. This directive was later implemented in the national legislation of the various European member states. The list of antibacterial feed additives that have been permitted in the European Community (EC) is shown in Table 1. This legislation has been amended on several occasions, and in non-EC

member countries other forms of legislation are in force, while in some other countries therapeutically used antibiotics such as tetracyclines and penicillins are still allowed. In 1986, Sweden, now a member of the EC, decided to ban all antibiotics for growth promotion, but ionophore antibiotics are still used as coccidiostats. In 1993, an initial report on the isolation of vancomycin (glycopeptide)-resistant enterococci (GRE) from animals appeared (30). Avoparcin, an antibiotic used only for growth promotion in animals, shows full cross-resistance with the human hospital drug vancomycin and partial cross-resistance with teicoplanin. All these antibiotics are glycopeptides. This is causing great concern because, following the first description of human infections with GRE in 1986 (214), these infections have become a serious problem in the hospital environment, especially in the United States (117). The occurrence of GRE in food animals was associated with the use of the glycopeptide antibiotic avoparcin in Europe (31, 43). Since 1997, this and several other antibiotic feed additives have been forbidden in EC member states (EC directive 97/6/EG and Commission regulation EC 2821/98) (Table 1). The discovery of GRE in animals and the growing resistance problem in gram-positive bacteria have also led to investigations of other antimicrobial growth promoters and related products, some of which are also under investigation or already in use for human therapy.

Many of the products reviewed here are not well known since they are not clinically available or not important in human therapy. Clinicians may be anxious that the use of antibacterials for animal growth promotion, largely unknown to them, is compromising their therapeutic means. The aim of this review is to summarize the data available on the lesser known antibiotics, giving special attention to their spectrum of antibacterial activity and their effects on the intestinal flora, resistance mechanisms, and prevalence of resistance. When available, data on pharmacokinetics and toxicity are presented. Since no resistance breakpoints are available for most of these antibiotics, the definition of susceptibility and resistance of bacteria to growth-promoting antibiotics is discussed first.

DIFFERENTIATING SUSCEPTIBILITY AND RESISTANCE TO GROWTH-PROMOTING ANTIBIOTICS

Differentiation between susceptibility and resistance of bacteria to antibiotics is commonly based on microbiological, pharmacological, and clinical criteria. The second criterion

implies that bacteria are susceptible to a given antibiotic when its attainable levels in blood can be expected to be higher than the MIC of the antibiotic for the bacterium. Since pharmacological data are lacking for most growth promoters and many of these drugs are not absorbed from the intestines and thus have no systemic effects, this criterion is not applicable. Clinical criteria cannot be applied either, since these antibiotics are generally not used therapeutically. Therefore, only the microbiological criterion is described and discussed here.

To determine susceptibility to a given antibiotic in this way, the distribution of MICs for strains belonging to a given species is analyzed, and when a monomodal distribution is evident, no acquired resistance is present. MICs in this monomodal Gaussian distribution can be more or less broadly distributed, in both lower and higher concentration ranges. Acquired resistance by this criterion is detected by loss of the normal monomodal distribution and is evident by tailing of the distribution, or by the appearance of a second group of MICs (bimodal distribution) or more extra distributions toward the higher concentration range. This criterion is used for bacterial species, since all strains of a given species react in a uniform way to an antibiotic, except when they have acquired resistance. The distribution ranges of susceptible and resistant strains may not always be easy to analyze since they may overlap. In these cases, the only way to determine susceptibility is to search for acquired resistance mechanisms or resistance-determining genes in these strains. A prerequisite for this is that resistance mechanisms and the genes encoding them should be known, which is not always the case. The difficulties encountered with respect to the differentiation between resistance and susceptibility as defined here are discussed in relation to each antibiotic reviewed.

There is no doubt that describing resistance to drugs other than those in clinical use is problematic. There are currently no standardized method and universally accepted interpretative criteria being applied to describe the antibiotic susceptibilities of isolates from the greater environment. The procedure to solve this problem described here is a proposal, not a consensus opinion. This is a significant question in need of a solution.

Bambermycin

The product. Bambermycin (synonyms: moenomycin, flavophospholipol, and flavomycin) is a glycolipid antibiotic produced by *Streptomyces* species including *S. bambergiensis*, *S. ghanaensis*, *S. geysirensis*, and *S. ederensis* (114, 115, 229). The product is manufactured as a complex of very similar components, of which moenomycin A, a phosphorus-containing glycolipid, is the main component (114, 209). Bambermycin is used only as a growth-promoting antibacterial in animal feeds.

Mechanism of action. Bambermycin inhibits peptidoglycan synthesis by inhibiting peptidoglycan polymerases through impairment of the transglycolase activities of penicillin-binding proteins (PBPs) (115, 220, 221, 225). This inhibition results in a specific block of the formation of the murein polysaccharide strands (127). The formation of the linear glycan strands of peptidoglycan is inhibited when the membrane intermediate *N*-acetylglucosaminyl-*N*-acetylmuramyl-(pentapeptide)-pyrophosphoryl-undecaprenol is used as a substrate (221). These PBPs are classified and designated by their differences in

molecular masses. PBP 1b, which is the polymerase responsible for this reaction in *Escherichia coli*, is inhibited by bambermycin. PBP 1a and PBP 3 of *E. coli* are also sensitive to the action of bambermycin (222). Recently, PBP 1c, which possesses transglycolase activity (190), was shown to be inhibited by bambermycin (225). In *Streptococcus pneumoniae*, PBP 2a is the target of bambermycin (167). The PBPs inhibited by bambermycin in other bacteria have not yet been determined. Differences in PBPs between *Enterococcus* species (244) might explain their differing susceptibility to bambermycin (40). PBPs are of cardinal importance in the action and in the resistance to β -lactam antibiotics, but since these drugs act on different PBPs, there is no cross-resistance between β -lactams and bambermycin (167).

Spectrum of activity. Bambermycin is active primarily against gram-positive organisms; to some extent, it also inhibits certain gram-negative bacteria, such as *Pasteurella* and *Brucella* (115). Its spectrum of activity covering staphylococci and streptococci is similar to that of penicillin G and in some respects to that of the macrolide antibiotics (139). Members of the *Enterobacteriaceae* are only slightly susceptible. MICs obtained for different bacteria are strongly medium dependent (39). The addition of blood, proteins, and fatty substances and variations in pH and inoculum size affect the in vitro susceptibility of gram-positive bacteria (39, 40, 230), thereby complicating the interpretation of susceptibility test results (40). *Clostridium perfringens* and many other clostridial species, bacteria of the *Enterococcus gallinarum* group (*E. gallinarum* and *E. casseliflavus*), and most species from the *E. faecium* group (*E. faecium*, *E. mundtii*, and *E. hirae*) show natural resistance to bambermycin (39, 40, 42, 46, 72, 79, 80, 81).

Prevalence of resistance. Few publications have dealt with the susceptibility testing of bacteria to bambermycin. The only data available are the MICs for enterococci, lactobacilli, *Staphylococcus* species, and clostridia (2, 42, 46, 71, 72, 80, 81, 112, 154). Acquired resistance has not yet been reported with certainty. Although most *E. faecium* strains were scored resistant in Danish and Dutch studies (2, 154), this resistance was probably natural or intrinsic. The few susceptible strains detected in these studies might have been wrongly identified, since phenotypic identification errors are relatively frequent with species other than *E. faecalis* (29). The application of arbitrary breakpoints (resistant when MIC is ≥ 16 $\mu\text{g/ml}$) and the fact that MICs of bambermycin are extremely dependent on the composition of the medium might also influence the resistance percentages reported. Few human bacterial strains have been tested against bambermycin. Methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* strains isolated from humans were both uniformly susceptible to bambermycin (128). In a large collection of *S. aureus* strains isolated from chickens and abattoir workers, no resistance to bambermycin was detected (112). Cross-resistance to other antimicrobials has not been reported.

Pharmacokinetics and toxicity. Bambermycin is absorbed poorly after oral administration in several animal species. A slight absorption was detected only when high doses were administered (32, 187, 230). When administered parenterally, bambermycin remains unchanged, being slowly excreted in the urine (187). In chickens, oral doses of 20 ppm did not produce residues in tissues or organs (160). Residues of bambermycin

could not be detected when high doses of the feed additive were administered (32, 187). No data are available on the active concentrations of the antibiotic in the intestines of animals.

Effects on intestinal flora. Bambermycin reduces the number of *C. perfringens* organisms in the intestines, a fact which contrasts with the relative insensitivity of this species to this agent in vitro (35, 38, 207). No influence was noted on the counts of enterococci, coliforms, and lactobacilli in the feces of broilers (38). In one study, the number of *E. coli* organisms in swine feces was decreased while the total numbers of enterococci remained the same. The number of *E. faecalis* strains, however, was dramatically decreased (219). Bambermycin in the feed did not affect intestinal *Salmonella* colonization in experimentally infected chickens (97, 116). This was in contrast to a recent study that reported reduced shedding of *Salmonella* in chickens (35) and other studies of calves and swine (67, 199). No effect has been seen on the incidence or degree of *Campylobacter* shedding (35).

Using germ-free mice inoculated with pig flora, it was demonstrated that bambermycin administered at 5 ppm diminished the numbers of antibiotic-resistant coliforms (65). Two in vivo studies, one with pigs receiving a feed containing bambermycin and the other with calves, demonstrated a decrease in the number of resistant *E. coli* organisms in the intestines (69, 219). Similar findings were noted with *Salmonella*-infected calves and swine (67, 199), while a decrease in the number of resistant *Salmonella enterica* serotype Typhimurium organisms in broilers could not be demonstrated (97).

In vitro, bambermycin inhibits the transfer of a wide variety of plasmids of different incompatibility groups containing a variety of different resistance determinants. An inhibitory effect was seen on the growth of *E. coli* containing these plasmids, although an increase of plasmid transfer occurred in a minority of strains (99, 139). A recent study described a significant inhibition by bambermycin of the transfer of the vancomycin resistance gene cluster-containing plasmid in *E. faecium* (182).

Streptogramins

The products. The streptogramins always consist of an A component and a B component which act synergistically. They belong to the MLS (macrolide-lincosamide-streptogramin) group of antibiotics. Both the streptogramin A and streptogramin B components are macrocyclic lactone peptolides, as are the macrolides. The lincosamides are devoid of a lactone ring (61, 204). The group A components are polyunsaturated cyclic peptolides, and the group B compounds are cyclic hexadepsipeptides (61). Until now, only three streptogramins have been marketed either as therapeutics or for growth promotion: virginiamycin, pristinamycin, and quinupristin/dalfopristin. Virginiamycin has been used both in topical preparations for human and veterinary medicine and as a growth promoter in animal feed. It is produced by *Streptomyces virginiae* as a natural mixture of two chemically different components, virginiamycin M (a streptogramin A component) and virginiamycin S (a streptogramin B component), that work synergistically. Pristinamycin, produced by *S. pristinaspiralis* (63), has been used orally and topically in human medicine in

a limited number of countries (143), most often in France (76). Quinupristin (streptogramin B component)/dalfopristin (streptogramin A component) was introduced into human medicine only very recently and is derived from the original pristinamycins (92). This compound is useful in treating infections due to vancomycin-resistant *E. faecium* and methicillin-resistant *S. aureus* (50, 145, 158, 159, 169, 185, 186, 211). It was approved in the United States in 1999 for the treatment of vancomycin-resistant *E. faecium* bacteremias, as well as of *S. aureus* and *Streptococcus pyogenes* skin and soft tissue infections.

Activity. The combination of the streptogramin A and B components acts by binding to the bacterial 23S rRNA of the 50S ribosomal subunit to form a stable dalfopristin (virginiamycin M) (A component)-ribosome-quinupristin (virginiamycin S) (B component) complex, which irreversibly inhibits protein synthesis, resulting in bacterial cell death (62). Individually, the components cause only bacteriostasis (62). The streptogramin A component inhibits the elongation phase in the ribosomal assemblage of the proteins (60). It interferes with the function of peptidyltransferase and also triggers a conformational change in the ribosome, which increases the affinity for the streptogramin B components (36). The streptogramin B component prevents the extension of polypeptides (peptide chain elongation) and induces the detachment of incomplete protein chains (57). The binding site of the B component overlaps with the binding site of the macrolide and lincosamide antibiotics (63, 235). The streptogramin antibiotics have a narrow spectrum of activity, including gram-positive bacteria (mainly staphylococci, streptococci, and enterococci) and some gram-negative cocci (101, 142). Not all enterococci have a similar susceptibility to streptogramins: *E. faecalis* is less susceptible than *E. faecium* (37, 64). Most gram-negative bacteria are naturally resistant, due to the impermeability of their cell wall (63). Quinupristin/dalfopristin is also active against *Toxoplasma gondii* (125).

Resistance genes and mechanisms. Resistance to streptogramins can be mediated by target site alteration, inactivation of the antibiotic, or active efflux of the antibiotic (183). The nomenclature of the resistance genes has recently been adapted (183). Target site alteration is mediated by the *erm* genes, affecting the binding of the B component of the streptogramins to the bacterial ribosome (140). The methylase encoded by these genes N⁶-demethylates a specific adenine residue at position 2058 (*E. coli* numbering) in 23S RNA (135). The combination of the A and B components, however, remains active, although this activity may be reduced in certain strains (53, 142). Cross-resistance with the macrolides and lincosamides (MLS_b phenotype of resistance expressed constitutively or inducibly) due to the overlapping binding sites of these antibiotics (157) is one characteristic of such combinations. Constitutively expressed MLS_b resistance is often due to deletions or insertions in the regulatory region of the *erm* genes (223, 236, 239).

A second resistance mechanism is mediated by inactivation of the antibiotic. In enterococci, this resistance mechanism can be mediated by an acetyltransferase that inactivates the A component of the streptogramin complex and is encoded by the *vat(D)* (formerly *satA*) gene (180). Recently, a new gene, *vat(E)* (formerly *satG*), that also encodes an acetyltransferase has been reported (240). Different *vat(E)* alleles have been

TABLE 2. Streptogramin resistance in enterococci of human origin

Species	Yr	Source	Resistance (%)	Reference
Not specified	1997	Human	30 ^a	217
<i>E. faecium</i>	1999	Human	3	19
<i>E. faecium</i>	1999	Human	8	189
<i>E. faecium</i>	1999	Human	0	188
<i>E. faecalis</i>	1999	Human	75	189
<i>E. faecalis</i>	1999	Human	26–43	19

^a Selective isolation procedure with MLS antibiotics in the media.

described and have been numbered from E-1 to E-3 (198). In staphylococci, resistance by inactivation of the A component can be mediated by an acetyltransferase: the VatA (formerly Vat), VatB, or VatC protein, encoded by the *vat(A)* (formerly *vat*) (11), *vat(B)* (12), or *vat(C)* (13) gene, respectively. The *vgb(A)* (formerly *vgb*) gene (16), encoding a hydrolase (lactonase) inactivating the B compound, is found in staphylococci and enterococci (119, 211). Inactivation of streptogramin antibiotics has also been described in lactobacilli (77), recently, the *vgb(B)* gene has been demonstrated in staphylococci (13).

A third mechanism of resistance involves the active efflux of streptogramins and is encoded by the *vga(A)* (formerly *vga*) gene (15) or the *vga(B)* gene (14) in staphylococci. The *vga(A)* gene encodes a putative ATP binding protein (11). A variant of this gene has been described recently (111). Another gene, *mrs(A)* [referring to both *mrs(A)* and *mrs(B)*], is found solely in staphylococci and encodes active transport of the streptogramin B component. The latter is inducible by erythromycin and also confers resistance to 14- and 15-membered macrolides (184). This gene is a putative member of the ATP binding cassette transporter superfamily (141, 183, 184, 247). Only recently, an *msr(A)*-like gene, designated *mrs(C)*, has been described and was shown to encode an efflux pump in enterococci (173).

Prevalence of resistance. Because there are not yet any clearly established interpretative virginiamycin susceptibility breakpoints for enterococcal strains, acquired resistance is difficult to assess by phenotypic means (41). In a study (197) in which a trimodal distribution of MICs for *E. faecium* strains was found, resistance genes were present only in the strains for which the MICs were highest. Strains with intermediate resistance to quinupristin/dalfopristin had drug MICs of 4 to 16 µg/ml. It is uncertain whether this is to be regarded as acquired resistance. Care should be taken in the interpretation of results obtained by different investigators (Tables 2 and 3), since different breakpoints might have been used. The search for resistance genes is a more reliable method for detecting streptogramin resistance (41).

In 1962, streptogramin resistance was described for the first time in staphylococci (181). No human streptogramin-resistant staphylococci were found in any countries except France and Algeria until 1983 (161). In these countries, resistance rates among human isolates of staphylococci remained low at ≤ 5% (84, 85, 143). Similar results were obtained with human isolates of *E. faecium* (19, 188, 189) (Table 2). However, the high resistance percentages published for *E. faecalis* (19, 188) should be interpreted cautiously since this species is only marginally susceptible to streptogramins. In addition, selective isolation procedures with MLS antibiotics incorporated in the media were used in some studies (217, 218), which explains in part the discrepancies seen between resistance percentages reported by different investigators (44). Among animal enterococci, resistance rates were especially high in strains isolated from poultry and pigs (Table 3). This high prevalence, however, was not reflected in strains isolated from pork. In staphylococci and lactobacilli, rates of resistance to streptogramins were generally low except among strains infecting pigs (2, 41, 42, 72, 73, 78, 79, 112). Resistance in *Clostridium perfringens* was low (72, 79, 231). Selection for streptogramin resistance

TABLE 3. Streptogramin resistance in enterococci of animal origin

Species	Yr	Source	Country	Resistance (%)	Reference
<i>E. faecium</i>	1982	Poultry	Belgium	0	80
Not specified	1997	Pigs	The Netherlands	75 ^a	217
Not specified	1998	Beef and pork	Germany	3	126
<i>E. faecium</i>	1998	Pigs	Denmark	47	2
<i>E. faecium</i>	1998	Poultry	Denmark	43	2
<i>E. faecium</i>	1998	Cattle	Denmark	8	2
<i>E. faecium</i>	1999	Animals and meat	Belgium	26	41
<i>E. faecium</i>	1998	Pigs	Denmark	99	2
<i>E. faecium</i>	1997	Pigs	Sweden	45 ^a	218
<i>E. faecium</i>	1995–1996	Pigs	The Netherlands	72 ^a	218
<i>E. faecium</i>	1998	Pigs	The Netherlands	42/64 ^b	154
<i>E. faecium</i>	1998	Poultry	The Netherlands	64/72 ^b	154
<i>E. faecium</i>	1998	Calves	The Netherlands	46/54 ^b	154
<i>E. faecium</i>	1998	Chicken meat	Belgium	58/58 ^b	41
<i>E. faecium</i>	1998	Pork	Belgium	0/0 ^b	42
<i>E. faecium</i>	1998	Cheese	Belgium	0/0 ^b	42
<i>E. faecium</i>	1998–1999	Broilers	Belgium	74	46
<i>E. faecium</i>	1998–1999	Pigs	Belgium	9	46
<i>E. faecium</i>	1998–1999	Ruminants	Belgium	0	46
<i>E. faecium</i>	1998–1999	Avian pets	Belgium	0	46
<i>E. faecium</i>	1998–1999	Mammalian pets	Belgium	3	46

^a Selective isolation with MLS antibiotics in the media.

^b Left percentage, virginiamycin; right percentage, quinupristin/dalfopristin

was found in the *E. faecalis* and *E. faecium* intestinal flora of chickens when they were fed a diet supplemented with virginiamycin (123). In turkeys, virginiamycin-resistant *E. faecium* strains were isolated increasingly during the administration of subtherapeutic levels of the antibiotic, with 100% of isolates becoming resistant by the end of the rearing period (238).

An investigation of Dutch streptogramin-resistant *E. faecium* strains revealed a high prevalence of the *vat(D)* (formerly *sataA*) gene among isolates from humans (51%), while in animal strains only 19% of these strains were *vat(D)* positive. In many resistant strains, no known resistance genes could be detected (119). In a Danish study, 25% of the strains from pigs and poultry contained the *vat(D)* gene (107). Further investigations of the Dutch animal and human strains demonstrated the presence of *vat(E)* in *vat(D)*-negative strains (110). The *vat(A)* (formerly *vat*) and *vgb(A)* (formerly *vgb*) genes were found combined with the *vat(E)* gene in only one human strain (110, 119). Another study demonstrated only the *vat(E)* gene among human *E. faecium* strains, while *vat(D)* and *vat(E)* were equally distributed in animal strains. In this investigation, no resistance genes could be detected in many resistant strains (197).

While the *vat(D)* gene was detected in about 10% of the Danish virginiamycin-resistant *E. faecium* strains from broilers and pigs, this gene was not detected in Finnish strains. Seventy-two percent of the Danish virginiamycin-resistant *E. faecium* strains from broilers carried the *vat(E)* gene, while all Finnish strains carried the *vat(E)* gene. In about 20% of the broiler strains and in the majority of the pig strains, no known resistance gene could be detected (6).

In *E. faecium* isolates of poultry origin, the *vat(E)* gene was frequently linked (in 74% of the strains) to the *erm(B)* gene (120). Only 2 strains were found to carry the *vat(B)* and *vat(C)* genes among 118 staphylococci of poultry origin (4). A large portion of human streptogramin-resistant staphylococcal strains contained multiple resistance genes: *vga(A)*, *vat(A)*, and *vgb(A)*. Some strains had only the *vat(B)* gene, while in others no resistance gene could be detected (17, 143). The combination of several resistance genes has also been described by Lina et al. (144).

Pharmacokinetics. Orally administered virginiamycin is not absorbed from the guts of animals (175). Likewise, no residues of virginiamycin could be found in kidneys, livers, or muscles of chickens fed virginiamycin (160). Pristinamycin is not water soluble and therefore not applicable parenterally (36). Quinu-pristin/dalfopristin, a water-soluble derivative of pristinamycin, is administered only by injection (36, 175). A new streptogramin under development (RPR 106972) showed good oral absorption (36).

Effects on intestinal flora. The number of *C. perfringens* organisms in the intestines of chickens was reduced by the addition of 55 ppm of virginiamycin to feed (217). Virginiamycin reduces the mortality and severity of necrotic enteritis caused by *C. perfringens* (98). No effects on the shedding of *Salmonella* in chickens or swine were noted (7, 8, 195). However, in combination with a competitive exclusion flora (a preparation based on whole cecal contents of healthy chickens), virginiamycin was shown to protect chickens against an *S. enterica* serotype Typhimurium infection (116).

Avilamycin

The product. Avilamycin belongs to the oligosaccharide (orthosomycin) group of antibiotics and is used only for growth promotion (130). Until recently, another antibiotic of this group, everninomycin, was investigated for use in human medicine (163, 233, 245). However, the development of this antibiotic has been stopped. Avilamycin is produced by *Streptomyces viridochromogenes* (47, 153). It is a mixture of several major and minor components (153).

Activity. Avilamycin acts through binding with the 30S subunit of the ribosome and interferes with the polypeptide-synthesizing function by affecting the attachment of aminoacyl-tRNA to the ribosomes (245). Recent findings, however, suggest that the antibiotic also binds, or solely binds, to the 50S subunit (56, 152).

Avilamycin and everninomycin are active mainly against gram-positive bacteria (95, 121, 128, 163). However, few reports have dealt with the in vitro activity of these antibiotics. Recently, the effective action of everninomycin against *Borrelia* species and *Legionella* species was demonstrated (70, 83).

Resistance. Resistance is associated with mutations in the L16 50S subunit ribosomal protein in *S. pneumoniae* (9), *E. faecalis*, and *E. faecium* (5). Spontaneous mutants of susceptible *S. pneumoniae* isolates also showed mutations in their 23S ribosomal DNA; these mutations were located at two different stems of the peptidyltransferase region of domain V (10). In the antibiotic-producing bacterium *S. viridochromogenes*, resistance is mediated by different mechanisms: a putative ATP-binding cassette transporter system, which confers a low level of resistance, and two rRNA methyltransferases, one of which confers a low level of resistance and one of which confers a high level of resistance (237). Another resistance mechanism, mediated by a methyltransferase (EmtA), has been described recently in an *E. faecium* strain from an animal. The gene encoding this resistance (*emtA*) was located on a plasmid-borne transposable element (149).

Acquired resistance to avilamycin in *E. faecium* and *E. faecalis* strains from animal sources has been reported only recently (2, 41, 46). Resistance rates were generally low, with the exception of broiler strains in Denmark (1, 2). Only one human strain, a clinical isolate of *S. pneumoniae* isolated in South Africa during a clinical trial, was found to be resistant to everninomycin (9). Full cross-resistance of avilamycin with everninomycin has been demonstrated (1). Searches for acquired resistance have been performed on only a limited number of bacterial species (2, 41, 72, 231). Among human enterococcal strains, no resistance has been reported (189), and no resistance has been found in *C. perfringens* strains from various food-producing animal species (72, 231).

Pharmacokinetics. Avilamycin administered orally at 60 ppm is excreted almost exclusively in the feces, and only very small residues are found in the tissues of swine and rats (148). Everninomycin can be administered only by intravenous injection (163).

Effects on intestinal flora. Few authors have investigated the influence of avilamycin on the gut flora. The number of *C. perfringens* organisms in chicken intestines was reduced by adding 10 ppm of avilamycin to the feed (87). Avilamycin also prevents necrotic enteritis caused by *C. perfringens* in broilers

(224). In a semiquantitative PCR study, the amount of PCR product was reduced in ileal and colon DNA extracts when the feed was supplemented with 40 ppm of avilamycin; these results indicate a reduction in the number of *C. perfringens* in the ileum and colon (215). The addition of avilamycin to the feed did not favor the colonization of *Salmonella* serotype Kedougou in young chickens (113). At relatively high doses, avilamycin reduced stress-induced postweaning diarrhea in piglets (130).

Bacitracin

The product. Bacitracin, a polypeptide antibiotic produced by *Bacillus licheniformis*, is a mixture of several major components—the most important of which are A, B and C—and at least 13 other minor components. Bacitracin is more stable as a zinc salt (166) and is used both as a growth promoter and in some topical preparations in human and veterinary medicine. It has also been tested, with limited success, for its applicability in the elimination of vancomycin-resistant enterococci (21, 55, 102, 165, 234).

Activity. Bacitracin forms a complex with C₅₅-isoprenyl pyrophosphate, a carrier for the *N*-acetylmuramyl peptapeptide intermediates for the synthesis of the peptidoglycan. Dephosphorylation by the C₅₅-isoprenyl pyrophosphatase is inhibited, thereby not allowing for the recycling of the carrier and inhibiting the bacterial cell wall formation. Bacitracin may also interfere with additional cellular processes (172, 193, 202, 203).

Bacitracin is active mainly against gram-positive bacteria, although many differences exist among the bacterial species (166). Its antibacterial spectrum is similar to that of the antibiotics of the penicillin group (226).

Resistance mechanisms. Resistance mechanisms have been described among gram-negative bacteria, in the bacitracin-producing organism *B. licheniformis*, and only very recently in other gram-positive bacteria (49, 54, 171, 172). The *bacA* gene in *E. coli* was found to encode a protein that increases isoprenol kinase activity. It was suggested that the *bacA* gene, which resides on the bacterial chromosome, confers resistance by phosphorylation of undecaprenol, thereby increasing the level of the carrier C₅₅-isoprenyl phosphate (49). Genes homologous to the *bacA* gene have been found in *S. aureus* and *S. pneumoniae*. Allelic replacement mutants of these strains showed an increased susceptibility to bacitracin, indicating that the *bacA* gene product is involved in C₅₅-isoprenyl phosphate recycling (54). It is unclear whether these genes play a role in acquired bacitracin resistance since they seem to be naturally present in a wide variety of bacterial species, including bacitracin susceptible ones. These genes might be related to the natural susceptibility level of these bacteria to bacitracin. In *B. licheniformis*, resistance was encoded in the *bcr* region (171). The Bcr proteins are components of an ATP binding transporter system which exports unidirectional bacitracin (171). Recently, a new bacitracin resistance gene, *bcrC_{ec}*, encoding a homologue to the resistance gene in *B. licheniformis*, was described in *E. coli* (109).

Prevalence of resistance. Problems with breakpoints between susceptibility and resistance have been encountered (41) and cause difficulties in interpreting resistance percentages. Rates of resistance to bacitracin as high as 60% were reported

in 1984 in *E. faecium* and *E. faecalis* from poultry (80, 81). More recently, only 3% of pig *E. faecalis* strains were found to be bacitracin resistant in Denmark (2), while in Belgium 16% of the strains from different animals and foods were resistant (41). In *E. faecium* isolates from pigs and poultry in Denmark (2), resistance rates were much higher (31 and 41%, respectively), but in Belgium they were similar to those of *E. faecalis* (41). Resistance rates among animal staphylococcal species are below 1% (2, 71, 112). While no resistance was found in *Lactobacillus* species from pigs, 10 and 24% of cattle and poultry strains, respectively, were resistant (78). In *Streptococcus suis*, bacitracin resistance was absent from 1968 to 1992. In 1992, 5.2% of the strains were resistant (3). In group L streptococci (*Streptococcus dysgalactiae*) from different animal species and in *Streptococcus porcinus* from pigs, no resistance to bacitracin could be detected (136, 194). Few animal *Clostridium* strains have been shown to be resistant (79, 79, 82). Bacitracin resistance in streptococci, enterococci, and staphylococci of human origin has been detected occasionally (89, 205). The resistance mechanisms in these gram-positive bacteria remain unknown to date.

Pharmacokinetics and toxicity. All bacitracins are nephrotoxic when administered parenterally. They are absorbed very little or not at all from the intestines, as demonstrated for rats, swine, and chickens (74, 94, 160). Because of this, no residues can be found in meat when the product is administered orally. Allergic reactions after absorption through skin lesions have been described occasionally in humans (166).

Effects on intestinal flora. Studies have demonstrated a decrease in the number of enterococci when bacitracin was included in the animal feed (27, 212). This decrease was due mainly to a decrease in the number of *E. faecalis* organisms (123). However, the number of *E. faecium* organisms increased compared to that in the control group during prolonged administration of the antibiotic (123). Necrotic enteritis caused by *C. perfringens* in chickens was prevented by the addition of bacitracin at doses of 55 to 110 ppm to the feed (174, 243). In addition, the number of *C. perfringens* organisms was decreased by the use of bacitracin (206). In a field trial, bacitracin appeared to reduce lesions of intestinal adenomatosis caused by *Lawsionia intracellularis* porcine in pigs (134). Bacitracin increases the colonization of *S. enterica* serotype Enteritidis in the ceca of chickens (150). Surprisingly, in combination with a competitive exclusion flora (cecal contents of healthy adult chickens or mixtures of bacteria cultured from ceca, sprayed over 1-day-old chickens to establish a stable intestinal flora), protection against *S. enterica* serotype Typhimurium infection was observed (116). On the other hand, colonization of serotype Infantis seemed to be inhibited by the administration of zinc bacitracin (164).

Ionophore Antibiotics

The products. Most ionophore antibiotics are produced by *Streptomyces* spp., although *Streptoverticillium*, *Nocardiosis*, *Nocardia*, and *Actinomadura* spp. are also known to produce them (33). Along with the natural products of microorganisms, several chemically modified ionophores exist. They belong to a vast group of ionophores, only a subset of which are used as growth promoters or in the prevention of infections in animals.

This subset can be divided into three major classes on the basis of their transport modes: the neutral ionophores, the carboxylic ionophores, and the channel-forming quasi-ionophores. Neutral ionophores, of which valinomycin is an example, do not have strong antibacterial activity and are not used as antibiotics. Carboxylic ionophores (also called polyether antibiotics) are subdivided into monovalent and divalent polyether antibiotics, depending on their preferential transport of monovalent or divalent cations (241). The ionophores incorporated into animal feed all belong to the carboxylic group. Examples of channel-forming quasi-ionophores include gramicidin and the polyene antibiotics, the best-known representatives of which are the antimycotic agents nystatin and amphotericin B. These antibiotics have a different mechanism of transmembrane transport: they open up ion conduction channels (177, 228). The ionophore antibiotics are active against parasites, including coccidia (*Eimeria*) and *Plasmodium* (25, 103, 104, 191), as well as against gram-positive organisms and mycoplasmas. They are not used therapeutically in humans. In animals the ionophores are used mainly for growth promotion and as "coccidiostats," in the prevention of coccidiosis (39, 51, 72, 81, 201, 228).

Monensin, lasalocid, salinomycin, narasin, and maduramycin are used in Europe. Only monensin (in bovines) and salinomycin (in pigs) are effectively registered as growth promoters. The other registered ionophores can be used in poultry feed as coccidiostats. Monensin is a monovalent carboxylic ionophorous polyether antibiotic produced by *Streptomyces cinnamonensis* that was previously referred to as monensic acid. It transports Na^+ more efficiently than K^+ (48, 108). Lasalocid is a divalent ionophore antibiotic (228). Although it transports bivalent ions such as Ca^{2+} and Mg^{2+} very well (176), it is also an efficient K^+ carrier (48). Salinomycin is a monovalent carboxylic ionophorous polyether antibiotic which is produced by the fermentation of a *Streptomyces albus* strain isolated from soil in Japan (146). It transports K^+ more efficiently than Na^+ . Narasin, also a monovalent ionophore, is produced by a strain of *Streptomyces aureofaciens* (75) and carries K^+ more efficiently than Na^+ (48, 52).

Monensin controls or prevents swine dysentery caused by *Brachyspira* (formerly *Serpulina*) *hyodysenteriae* (131) and has been proven active against an *Enterococcus*-like pathogen in rainbow trout (51). Lasalocid can be used in the treatment of *Mycoplasma* infections in chickens (200). Salinomycin is effective in controlling swine dysentery (S. C. Kyriakis, K. Sarris, A. C. Tsinas, and J. C. Papatsas, Proc. 12th Int. Vet. Soc. Cong., p. 289, 1992) and porcine intestinal adenomatosis (131), and it can be helpful in controlling *C. perfringens* type A infections in growing pigs (133). Care should be taken with the dosage of these products. With elevated levels, growth performance is impaired (124).

Mechanism of action. Polyether antibiotics interfere with the natural ion transport systems of both prokaryotic and eukaryotic cells. Ionophores lower the energy barrier necessary for the transmembrane transport of ions and catalyze an electroneutral cation-proton exchange across the barrier. Consequently, they abolish the gradients of Ca^{2+} , Mg^{2+} , K^+ , and Na^+ , causing cell death (242). The cell walls of most gram-negative bacteria do not permit the penetration of hydropho-

bic molecules with molecular weights of 600 and above and thus are not susceptible to the action of ionophores (242).

Resistance. A resistance mechanism has been described on only one occasion. *Streptomyces longisporoflavus*, which produces tetroneasin, a polyether antibiotic not used in animal feed, contains genes encoding an ATP-dependent efflux system which defends the bacterium against the action of tetroneasin (147). The slight increases of MICs for resistant strains (45) indicate that an efflux mechanism might be responsible in these strains. This needs further investigation. MICs of ionophores for several bacteria should be interpreted cautiously. One medium that imitates a more natural environment (a medium containing feed particles) demonstrated a relative insensitivity of several bacteria to ionophores (151). The pH of the medium can also influence the activity of ionophores (58). The addition of blood and incubation in a CO_2 -enriched atmosphere alter MIC results (39). Serum proteins inhibit the ion transport capacities of ionophores in erythrocytes and the antimalaria activities of ionophores (100). It has been postulated, based on the fact that medium composition has a large influence on MICs, that MICs do not provide accurate assessment of microbial growth inhibition by ionophores in vivo (58). Resistance to ionophores has been described in *Staphylococcus hyicus* isolated from pigs and *S. aureus* and coagulase-negative staphylococci isolated from cattle (2). Decreased susceptibility both in *E. faecium* and in *E. faecalis* has been reported in Belgium (45): resistance or decreased susceptibility of *E. faecium* was as high as 75% in poultry strains and 33% in strains from swine feces. The rates were much lower in *E. faecalis*, with 33% of the poultry strains and 8% of the porcine strains showing decreased susceptibility. Resistance rates in The Netherlands were similar (154). There was no complete cross-resistance between the ionophores tested. While certain strains showed decreased susceptibility to salinomycin and narasin, this was not the case for monensin and lasalocid (45). The reason for this incomplete cross-resistance remains unclear. Acquired resistance to ionophores has not yet been reported either for clostridia (33, 34, 72, 79, 82, 129, 228) or for other anaerobic bacteria (228).

Pharmacokinetics and toxicity. The ion transport capacity of ionophores does not discriminate between bacterial and mammalian membranes. Since they have good oral absorption (24, 191), these products are quite toxic for mammals and birds. Several accidents have been reported with overdoses of ionophores in mammals, mostly involving acute intoxications, although reports of chronic intoxications have also appeared (156, 162, 170). Horses and rabbits seem to be particularly susceptible to ionophore intoxications (22). Both acute and chronic intoxication have been described, especially with maduramycin in cattle fed poultry litter (192). Ionophore intoxication is also well known in birds (18, 26, 28, 179). Not all bird species are equally sensitive to the toxicity of ionophores. Turkeys, guinea fowl, and Japanese quail seem to be more susceptible to monensin intoxication than other birds are (106, 179).

Ionophores are incompatible with several therapeutic antibiotics. Incompatibilities between ionophores and tiamulin, chloramphenicol, erythromycin, oleandomycin, and certain sulfonamides have been demonstrated (213, 227). Some antioxidants (XAX-M, duokvin, TD) are also incompatible with some ionophores (178). Embryo toxicity has been described for

salinomycin in chicken eggs (23). This ionophore can be transported from the laying hen to the egg.

Effects on intestinal flora. Few studies have been performed on the antibacterial effects of ionophores in the intestines. No effect of monensin was observed on the cecal colonization ability of *Salmonella* (150), and no resistance selection in coliforms and streptococci could be demonstrated in chickens (96). This product inhibits *C. perfringens* (types A and C) in chickens and turkeys, suggesting that it could be used to prevent necrotic enteritis (86, 207). Narasin has also been effective in the treatment and prevention of *C. perfringens* infections in chickens (86, 224). In pigs, salinomycin reduces the lesions and the presence of *Lawsonia intracellularis*, causing proliferative enteropathy in the intestines in fattening pigs (Kyriakis et al., Proc. 12th Int. Vet. Soc. Congr., 1992).

Other Growth-Promoting Antibacterials

Quinoxalines. Carbadox and olaquidox are synthetic antibacterials that act by inhibiting DNA synthesis. They are active mainly against gram-negative bacteria (88, 210). Although these quinoxalines sometimes are regarded as growth promoters, they are used mainly in the prevention of swine dysentery caused by *Brachyspira hyodysenteriae* and thus are not discussed here.

Efrotomycin. Efrotomycin, an elfamycin antibiotic, is used solely as a growth promoter. However, its usage has been very limited to date. For reasons unknown to the authors, this product has not been marketed by the manufacturer to any extent in Europe. Efrotomycin belongs to the kirromycin-like class of antibiotics and is produced by *Nocardia lactamdurans*. It is an *N*-methylhydroxypridone glycoside (59, 66, 138, 232). The molecular structure consists of a central dihydroxytetrahydrofurane ring, a pyridone ring system, and a goldimic acid (168). Efrotomycin inhibits bacterial growth by the formation of a nondissociable ribosome elongation factor Tu (EF-Tu) complex (137, 246). The product is inactive against gram-negative bacteria because it cannot penetrate the cell, although EF-Tu of gram-negative bacteria is inhibited by efrotomycin in cell-free systems (105). Some activity against *Neisseria gonorrhoeae* and *Haemophilus influenzae* has been demonstrated (138). Streptococcal species are relatively insensitive (138). Efrotomycin is inactive against staphylococci (105, 138), some *Lactobacillus* species (138), certain enterococcal species (155), and some *Bacillus* species (138) due to the insensitivity of their EF-Tu to this antibiotic. The susceptibility patterns of the various enterococcal species seem to be the inverse of those of bambarmycin, with the species of the *E. faecium* group (*E. faecium*, *E. durans*, *E. hirae*, and *E. mundtii*) being susceptible and the other species being resistant (155). Efrotomycin has good in vitro activity against *C. difficile* and *C. perfringens* (59, 208). The finding in laboratory experiments of mutant *E. coli* and *B. subtilis* strains resistant to elfamycin antibiotics has been described previously (196, 216). Efrotomycin is rapidly absorbed orally (93). It had no influence on *S. enterica* serotype Typhimurium prevalence, shedding, and resistance profile in swine (118). It diminished the numbers of *C. perfringens* organisms in the ileal contents of chicks (208).

CONCLUDING REMARKS

Only some of the antibiotics that are used today or that have been used in the past for growth promotion in animal husbandry have been well investigated. These include the antibiotics of therapeutic importance to humans. For others, a large body of knowledge is available indirectly because related products are used in human medicine. The spectrum of the growth-promoting antibiotics, with the exception of the quinoxalines, is limited to gram-positive bacteria. Nowadays, much research is being done on products active on these organisms since major problems exist in the therapy of infections caused by multiresistant gram-positive bacteria in humans. New chemical adaptations to products now used solely for growth promotion might be useful in therapy dealing with multiresistant gram-positive bacterial infections. The fact that some antibiotics treated in this review are used solely in animals offers opportunities to study transfers of resistance-determining genes between different ecosystems. Only fragmentary information is available on the possible spread of resistance genes from animals to humans.

REFERENCES

1. Aarestrup, F. M. 1998. Association between decreased susceptibility to a new antibiotic for treatment of human diseases, everninomycin (SCH 27899), and resistance to an antibiotic used for growth promotion in animals, avilamycin. *Microb. Drug Resist.* **4**:137-141.
2. Aarestrup, F. M., F. Bager, N. E. Jensen, M. Madsen, A. Meyling, and H. K. Wegener. 1998. Surveillance of antimicrobial resistance in bacteria isolated from food animals to growth promoters and related therapeutic agents in Denmark. *APMIS* **106**:606-622.
3. Aarestrup, F. M., S. R. Rasmussen, K. Arturson, and N. E. Jensen. 1998. Trends in the resistance to antimicrobial agents of *Streptococcus suis* isolates from Denmark and Sweden. *Vet. Microbiol.* **63**:71-78.
4. Aarestrup, F. M., Y. Agerso, P. Ahrens, J. C. O. Jorgensen, M. Madsen, and L. B. Jensen. 2000. Antimicrobial susceptibility and presence of resistance genes in staphylococci from poultry. *Vet. Microbiol.* **74**:353-364.
5. Aarestrup, F. M., and L. B. Jensen. 2000. Presence of variations in ribosomal proteins L16 corresponding to the susceptibility to oligosaccharides (avilamycin and everninomycin) *Antimicrob. Agents Chemother.* **44**:3425-3427.
6. Aarestrup, F. M., H. Kruse, E. Tast, A. M. Hammerum, and L. B. Jensen. 2000. Associations between the use of antimicrobial agents for growth promotion and the occurrence of resistance among *Enterococcus faecium* from broilers and pigs in Denmark, Finland, and Norway. *Microb. Drug Resist.* **6**:63-70.
7. Abou-Youssef, M. H., C. J. Di Cuollo, S. M. Free, and G. C. Scott. 1983. The influence of a feed additive level of virginiamycin on the course of an experimentally induced *Salmonella typhimurium* infection in broilers. *Poult. Sci.* **62**:30-37.
8. Abou-Youssef, M. H., C. J. Di Cuollo, C. R. Miller, and G. C. Scott. 1979. Influence of a sub-therapeutic level of virginiamycin in feed on the incidence and persistence of *Salmonella typhimurium* in experimentally infected swine. *J. Anim. Sci.* **49**:128-133.
9. Adrian, P. V., W. Zhao, T. A. Black, K. J. Shaw, R. S. Hare, and K. P. Klugman. 2000. Mutations in ribosomal protein L16 conferring reduced susceptibility to everninomycin (SCH27899): Implications for mechanism of action. *Antimicrob. Agents Chemother.* **44**:732-738.
10. Adrian, P. V., C. Mendrick, D. Loebenberg, P. McNicholas, K. J. Shaw, K. P. Klugman, R. S. Hare, and T. A. Black. 2000. Everninomycin (SCH27899) inhibits a novel ribosome target site: analysis of 23S ribosomal DNA mutants. *Antimicrob. Agents Chemother.* **44**:3101-3106.
11. Allignet, J., V. Loncle, C. Simenel, M. Delepierre, and N. El Sohl. 1993. Sequence of a staphylococcal gene *vat*, encoding an acetyl transferase inactivating the A-type components of virginiamycin-like antibiotics. *Gene* **130**:91-98.
12. Allignet, J., and N. El Sohl. 1995. Diversity among the Gram-positive acetyltransferases inactivating streptogramin A and structurally related compounds and characterization of a new staphylococcal determinant, *vatB*. *Antimicrob. Agents Chemother.* **39**:2027-2036.
13. Allignet, J., N. Liasinne, and N. El Sohl. 1998. Characterization of a staphylococcal plasmid related to pUB110 and carrying two novel genes, *vatC* and *vgbB*, encoding resistance to streptogramin A and B and similar antibiotics. *Antimicrob. Agents Chemother.* **42**:1794-1798.
14. Allignet, J., and N. El Sohl. 1997. Characterization of a new staphylococcal

- gene, *vgaB*, encoding a putative ABC transporter conferring resistance to streptogramin A and related compounds. *Gene* **202**:133–138.
15. Allignet, J., V. Loncle, and N. El Sohl. 1992. Sequence of a staphylococcal plasmid gene, *vga*, encoding a putative ATP-binding protein involved in resistance to virginiamycin A-like antibiotics. *Gene* **117**:45–51.
 16. Allignet, J., V. Loncle, P. Mazodier, and N. El Sohl. 1988. Nucleotide sequence of a staphylococcal plasmid gene, *vgb*, encoding a hydrolase inactivating the B components of virginiamycin-like antibiotics. *Plasmid* **20**:271–275.
 17. Allignet, J., S. Aubert, A. Morvan, and N. El Sohl. 1996. Distribution of genes encoding resistance to streptogramin A and related compounds among staphylococci resistant to these antibiotics. *Antimicrob. Agents Chemother.* **40**:2523–2528.
 18. Andreasen, J. R., and J. H. Schleifer. 1995. Salinomycin toxicosis in male turkey breeders. *Avian Dis.* **39**:638–642.
 19. Andrews, J., J. Ashby, G. Jevons, N. Lines, and R. Wise. 1999. Antimicrobial resistance in Gram-positive pathogens isolated in the UK between October 1996 and January 1997. *J. Antimicrob. Chemother.* **43**:689–698.
 20. Anonymous. 1968. Joint Committee on the use of antibiotics in animal husbandry and veterinary medicine. Report. Her Majesty's Stationery Office, London, United Kingdom.
 21. Armstrong-Evans, M., M. Litt, M. A. McArthur, B. Willey, D. Cann, S. Liska, S. Nusinowitz, R. Gould, A. Blacklock, D. E. Low, and A. McGeer. 1999. Control of transmission of vancomycin-resistant *Enterococcus faecium* in a long-term-care facility. *Infect. Control Hosp. Epidemiol.* **20**:312–317.
 22. Arts, H. T. 1991. Intoxicatie door een ionophoor anticoccidium in een commercieel konijnenbedrijf. *Tijdschr. Diergeneesk.* **116**:504–507.
 23. Atef, M., A. A. Shalaby, A. Khafagy, and M. A. Abo-Norage. 1989. Fetotoxicity of some anticoccidial drugs in chickens. *Dtsch. Tierärztl. Wochenschr.* **96**:296–298.
 24. Atef, M., A. Ramadan, S. A. H. Youssef, and K. Abo El-Souod. 1993. Kinetic disposition, systemic bioavailability and tissue distribution of salinomycin in chickens. *Res. Vet. Sci.* **54**:179–183.
 25. Augustine, P. C., C. K. Smith II, D. H. Danforth, and D. Ruff. 1987. Effect of ionophorous anticoccidials on invasion and development of *Eimeria*: comparison of sensitive and resistant isolates and correlation with drug uptake. *Poult. Sci.* **66**:960–965.
 26. Baird, G. J., G. L. Caldwell, I. S. Peek, and D. A. Grant. 1997. Monensin toxicity in a flock of ostriches. *Vet. Rec.* **140**:624–626.
 27. Barnes, E. M., G. C. Mead, C. S. Impey, and B. W. Adams. 1978. The effect of dietary bacitracin on the incidence of *Streptococcus faecalis* subspecies *liquefaciens* and related streptococci in the intestines of young chickens. *Br. Poult. Sci.* **19**:713–723.
 28. Bartov, I. 1994. Effect of growth promoters on monensin toxicity in broiler chicks. *Br. Poult. Sci.* **35**:123–133.
 29. Bascomb, S., and M. Manafi. 1998. Use of enzyme tests in characterization and identification of aerobic and facultatively anaerobic Gram-positive cocci. *Clin. Microbiol. Rev.* **11**:318–340.
 30. Bates, J., J. Z. Jordans, and J. B. Selkon. 1993. Evidence for an animal origin of vancomycin-resistant enterococci. *Lancet* **342**:490–491.
 31. Bates, J. 1997. Epidemiology of vancomycin-resistant enterococci in the community and relevance of farm animals to human infections. *J. Hosp. Infect.* **37**:89–101.
 32. Bauer, F., and G. Dost. 1966. Moenomycin in animal nutrition, p. 749–752. *Antimicrob. Agents Chemother.* **1965**.
 33. Benno, Y., K. Endo, N. Shiragami, and T. Mitsuoka. 1988. Susceptibility of fecal anaerobic bacteria from pigs and chickens to five polyether antibiotics for growth promotion. *Jpn. J. Vet. Sci.* **50**:783–790.
 34. Benno, Y., K. Endo, and T. Mitsuoka. 1988. Isolation of fecal *Clostridium perfringens* from broiler chickens and their susceptibility to eight antimicrobial agents for growth promotion. *Jpn. J. Vet. Sci.* **50**:832–834.
 35. Bolder, N. M., J. A. Wagenaar, F. F. Putirulan, K. T. Veldman, and M. Sommer. 1999. The effect of flavophospholipol (Flavomycin®) and salinomycin sodium (Sacox®) on the excretion of *Clostridium perfringens*, *Salmonella enteritidis*, and *Campylobacter jejuni* in broilers after experimental infection. *Poult. Sci.* **78**:1681–1689.
 36. Bouanchaud, D. H. 1997. Streptogramins: from parenteral to oral, p. 51–66. *In* S. H. Zinner, L. S. Young, J. F. Acar, and H. C. Neu (ed.), *Expanding indications for the new macrolides, azalides, and streptogramins*. Marcel Dekker, Inc., New York, N.Y.
 37. Bouanchaud, D. H. 1997. In-vitro and in-vivo antibacterial activity of quinupristin/dalfopristin. *J. Antimicrob. Chemother.* **39**(Suppl. A):15–21.
 38. Brenes, A., J. Trevino, C. Centeno, and P. Yuste. 1989. Influence of peas (*Pisum sativum*) as a dietary ingredient and flavomycin supplementation on the performance and intestinal microflora of broiler chicks. *Br. Poult. Sci.* **30**:81–89.
 39. Butaye, P., L. A. Devriese, and F. Haesebrouck. 1998. Effects of different test conditions on MICs of food animal growth-promoting antibacterial agents for enterococci. *J. Clin. Microbiol.* **36**:1907–1911.
 40. Butaye, P., L. A. Devriese, and F. Haesebrouck. 2000. Effects of different medium supplements on the MICs of the growth-promoting antibiotic bambarmycin against enterococci. *J. Antimicrob. Chemother.* **46**:713–716.
 41. Butaye, P., L. A. Devriese, and F. Haesebrouck. 1999. Phenotypic distinction in *Enterococcus faecium* and *Enterococcus faecalis* strains between susceptibility and resistance to growth-enhancing antibiotics. *Antimicrob. Agents Chemother.* **43**:2569–2570.
 42. Butaye, P., K. Van Damme, L. A. Devriese, L. Van Damme, M. Baele, S. Lauwers, and F. Haesebrouck. 2000. In vitro susceptibility of *Enterococcus faecium* isolated from food to growth-promoting and therapeutic antibiotics. *Int. J. Food Microbiol.* **54**:181–187.
 43. Butaye, P., L. A. Devriese, and F. Haesebrouck. 1999. Glycopeptide resistance in *Enterococcus faecium* strains from animals and humans. *Rev. Med. Microbiol.* **10**:235–243.
 44. Butaye, P., L. A. Devriese, and F. Haesebrouck. 1999. Comparison of direct and enrichment methods for the selective isolation of vancomycin-resistant enterococci from feces of pigs and poultry. *Microb. Drug Resist.* **5**:131–134.
 45. Butaye, P., L. A. Devriese, and F. Haesebrouck. 2000. Incomplete cross resistance against ionophores in *Enterococcus faecium* and *Enterococcus faecalis* strains from pigs and poultry. *Microb. Drug Resist.* **6**:59–61.
 46. Butaye, P., L. A. Devriese, and F. Haesebrouck. 2001. Differences in antibiotic resistance patterns of *Enterococcus faecalis* and *Enterococcus faecium* from farm and pet animals. *Antimicrob. Agents Chemother.* **45**:1374–1378.
 47. Buzetti, F., F. Eisenberg, H. N. Grant, W. Keller-Schierlein, W. Voser, and H. Zähler. 1968. Avilamycin. *Experientia* **24**:320–323.
 48. Caffarel-Mendez, S., C. Demuynck, and G. Jeminet. 1987. Etude "in vitro" de quelques antibiotiques ionophores et de certains de leurs dérivés. II. Caractérisation des propriétés ionophores des composés dans un système modèle, pour les ions Na⁺ et K⁺. *Reprod. Nutr. Dev.* **27**:921–928.
 49. Cain, B. D., P. J. Norton, W. Eubanks, H. S. Nick and C. M. Allen. 1993. Amplification of the *bacA* gene confers bacitracin resistance to *Escherichia coli*. *J. Bacteriol.* **175**:3784–3789.
 50. Carbon, C. 1999. Costs of treating infections caused by methicillin-resistant staphylococci and vancomycin-resistant enterococci. *J. Antimicrob. Chemother.* **44**(Topic A):31–36.
 51. Carson, J., and P. Statham. 1993. The inhibition by ionophores *in vitro* of an *Enterococcus*-like pathogen of rainbow trout, *Oncorhynchus mykiss*. *Vet. Microbiol.* **36**:253–259.
 52. Caughey, B., G. R. Painter, A. F. Drake, and W. A. Gibbons. 1986. The role of molecular confirmation in ion capture by carboxylic ionophores: a circular dichroism study of narasin A in single phase solvents and liposomes. *Biochim. Biophys. Acta* **854**:109–116.
 53. Chabbert, Y. A., and P. Courvalin. 1971. Synergie des composants des antibiotiques du groupe de la streptogramin. *Pathol. Biol.* **19**:613–619.
 54. Chalker, A. F., K. A. Ingraham, R. D. Lunsford, A. P. Bryant, J. Bryant, N. G. Wallis, J. P. Broskey, S. C. Pearson, and D. J. Holmes. 2000. The *bacA* gene, which determines bacitracin susceptibility in *Streptococcus pneumoniae* and *Staphylococcus aureus*, is also required for virulence. *Microbiology* **146**:1547–1553.
 55. Chia, J. K., M. Nakata, S. S. Park, R. P. Lewis, and B. McKee. 1995. Use of bacitracin therapy for infection due to vancomycin-resistant *Enterococcus faecium*. *Clin. Infect. Dis.* **21**:1520.
 56. Champney, W. S., and C. L. Tober. 2000. Everninomycin (SCH 27899) inhibits both translation and 50S ribosomal subunit formation in *Staphylococcus aureus* cells. *Antimicrob. Agents Chemother.* **44**:1413–1417.
 57. Chinali, G., E. Nyssen, M. Di Giambattista, and C. Cocito. 1988. Action of erythromycin and virginiamycin S on polypeptide synthesis in cell-free systems. *Biochim. Biophys. Acta* **951**:42–52.
 58. Chow, J. M., and J. B. Russell. 1990. Effect of ionophores and pH on growth of *Streptococcus bovis* in batch and continuous culture. *Appl. Environ. Microbiol.* **56**:1588–1593.
 59. Clabots, C. R., C. J. Shanholzer, L. R. Peterson, and D. N. Gerding. 1987. In vitro activity of efrotomycin, ciprofloxacin, and six other antimicrobials against *Clostridium difficile*. *Diagn. Microbiol. Infect. Dis.* **6**:49–52.
 60. Cocito, C., H. Voorma, and L. Bosch. 1974. Interference of virginiamycin M with the initiation and the elongation of peptide chains in cell-free systems. *Biochim. Biophys. Acta* **340**:285–298.
 61. Cocito, C. 1979. Antibiotics of the virginiamycin family, inhibitors which contain synergistic components. *Microbiol. Rev.* **43**:145–198.
 62. Cocito, C., M. Di Giambattista, E. Nyssen, and P. Vannuffel. 1997. Inhibition of protein synthesis by streptogramins and related antibiotics. *J. Antimicrob. Chemother.* **39**(Suppl. A):7–13.
 63. Cocito, C., M. Di Giambattista, E. Nyssen, and P. Vannuffel. 1997. The molecular mechanism of action of streptogramins and related antibiotics, p. 145–172. *In* S. H. Zinner, L. S. Young, J. F. Acar, and H. C. Neu (ed.), *Expanding indications for the new macrolides, azalides, and streptogramins*. Marcel Dekker, Inc., New York, N.Y.
 64. Collins, L. A., G. J. Malanoski, G. M. Eliopoulos, C. B. Wennersten, M. J. Ferraro, and R. C. Moellering, Jr. 1993. In vitro activity of RP59500, an injectable streptogramin antibiotic, against vancomycin-resistant gram-positive organisms. *Antimicrob. Agents Chemother.* **37**:598–601.
 65. Corpet, D. E. 1984. The effect of bambarmycin, carbadox, chlortetracycline and olaquinox on antibiotic resistance in intestinal coliforms: a new animal model. *Ann. Microbiol.* **135A**:329–339.

66. Cover, W. H., A. C. Kirpekar, H. George, and R. W. Stieber. 1991. Calcium inhibition of efrotomycin production by *Nocardia lactamdurans*. J. Ind. Microbiol. 7:41-44.
67. Dealy, J., and M. W. Moeller. 1976. Influence of bambermycins on *Salmonella* infection and antibiotic resistance in swine. J. Anim. Sci. 42:1331-1336.
68. Reference deleted.
69. Dealy, J., and M. W. Moeller. 1977. Influence of bambermycins on *Escherichia coli* and antibiotic resistance in calves. J. Anim. Sci. 42:1239-1242.
70. Dever, L. L., C. V. Torigan, and A. G. Barbour. 1999. In vitro activities of the evernimycin SCH 27899 and other newer antimicrobial agents against *Borrelia burgdorferi*. Antimicrob. Agents Chemother. 43:1773-1775.
71. Devriese, L. A. 1980. Sensitivity of staphylococci from farm animals to antibacterial agents used for growth promotion and therapy, a ten year study. Ann. Rech. Vet. 11:399-408.
72. Devriese, L. A., G. Daube, J. Hommez, and F. Haesebrouck. 1993. In vitro susceptibility of *Clostridium perfringens* isolated from farm animals to growth-enhancing antibiotics. J. Appl. Microbiol. 75:55-57.
73. Devriese, L. A. 1976. In vitro susceptibility and resistance of animal staphylococci to macrolide antibiotics and related compounds. Ann. Rech. Vet. 7:65-74.
74. Donoso, G., G. O. Craig, and R. S. Baldwin. 1970. The distribution and excretion of zinc bacitracin-¹⁴C in rats and swine. Toxicol. Appl. Pharmacol. 17:366-374.
75. Droumev, D. 1983. Review of antimicrobial growth promoting agents available. Vet. Res. Commun. 7:85-99.
76. Dublanquet, A., C. J. Soussy, F. Squinazi, and J. Duval. 1977. Résistance de *Staphylococcus aureus* aux straptogramines. Ann. Microbiol. 128A:277-287.
77. Dutta, G. N., and L. A. Devriese. 1981. Degradation of macrolide-lincosamide-streptogramin antibiotics by *Lactobacillus* strains from animals. Ann. Microbiol. 132:51-57.
78. Dutta, G. N., and L. A. Devriese. 1981. Sensitivity and resistance to growth promoting agents in animal lactobacilli. J. Appl. Bacteriol. 51:283-288.
79. Dutta, G. N., and L. A. Devriese. 1980. Susceptibility of *Clostridium perfringens* of animal origin to fifteen antimicrobial agents. J. Vet. Pharmacol. Therp. 3:227-236.
80. Dutta, G. N., and L. A. Devriese. 1982. Susceptibility of fecal streptococci of poultry origin to nine growth promoting agents. Appl. Environ. Microbiol. 44:832-837.
81. Dutta, G. N., and L. A. Devriese. 1984. Observations on the in vitro sensitivity of Gram-positive intestinal bacteria of farm animals to growth promoting antibacterials. J. Appl. Bacteriol. 56:117-123.
82. Dutta, G. N., L. A. Devriese, and P. Van Assche. 1983. Susceptibility of clostridia from farm animals to 21 antimicrobial agents including some used for growth promotion. J. Antimicrob. Chemother. 12:347-356.
83. Edelstein, P. H., and M. A. C. Edelstein. 1999. In vitro activity of SCH 27899 (ziracin) against *Legionella* species. Diagn. Microbiol. Infect. Dis. 33:59-62.
84. El Sohl, N., R. Bismuth, J. Allignet, and J. M. Fouace. 1984. Résistance à la pristinamycine (ou virginiamycine) des souches de *Staphylococcus aureus*. Pathol. Biol. 32:362-368.
85. El Sohl, N., J. Allignet, V. Loncle, S. Aubert, A. Casetta, and A. Morvan. 1993. Actualités sur les staphylococques résistants aux synergistines (pristinamycine). Lett. Infectiol. 20:608-615.
86. Elwinger, K., C. Schneitz, E. Berndtson, O. Fossum, B. Teglóf, and B. Engström. 1992. Factors affecting the incidence of necrotic enteritis, caecal carriage of *Clostridium perfringens* and bird performance in broiler chickens. Acta Vet. Scand. 33:369-378.
87. Elwinger, K., E. Berndtson, B. Engström, O. Fossum, and L. Waldenstedt. 1998. Effect of antibiotic growth promoters and anticoccidials on growth of *Clostridium perfringens* in the caeca and on performance of broiler chickens. Acta Vet. Scand. 39:433-441.
88. English, A. R., and C. M. Dunegan. 1970. Quinoxalines-1, 4-diN oxides. Inhibition of deoxyribonucleic acid synthesis in *Escherichia coli* by 2,3-dihydroxymethyl-quinoxaline-1, 4-diN-oxide. Proc. Soc. Exp. Biol. Med. 133:398-400.
89. Everett, S. L., R. P. Kowalski, L. M. Karenchak, D. Landsittel, R. Day, and Y. J. Gordon. 1995. An in vitro comparison of the susceptibilities of bacterial isolates from patients with conjunctivitis and blepharitis to newer and established topical antibiotics. Cornea 14:382-387.
90. Ewing, W. N., and D. J. A. Cole. 1994. The living gut. An introduction to microorganisms in nutrition. Context, Dungannon, Ireland.
91. Feighner, S. D., and M. P. Dashkevich. 1987. Subtherapeutic levels of antibiotics in poultry feeds and their effects on weight gain, feed efficiency, and bacterial cholytaurine hydrolase activity. Appl. Environ. Microbiol. 53:331-336.
92. Finch, R. G. 1997. A review of the clinical use of macrolides and streptogramins, p. 3-26. In S. H. Zinner, L. S. Young, J. F. Acar, and H. C. Neu (ed.), Expanding indications for the new macrolides, azalides, and streptogramins. Marcel Dekker, Inc., New York, N.Y.
93. Frost, B. M., M. E. Valiant, B. Weissberger, and E. L. Dulaney. 1976. Antibacterial activity of efrotomycin. J. Antibiot. 24:1083-1091.
94. Froyshov, O., S. Pedersen, and K. Hove. 1986. Absorption, metabolism and excretion of zinc C¹⁴-bacitracin fed to young pigs. J. Anim. Physiol. Anim. Nutr. 55:100-110.
95. Fuchs, P. C., A. L. Barry, and S. D. Brown. 1999. In vitro activities of SCH27899 alone and in combination with 17 other antimicrobial agents. Antimicrob. Agents Chemother. 43:2996-2997.
96. George, B. A., A. M. Ford, D. J. Fagerberg, and C. L. Quarles. 1981. Influence of salinomycin on antimicrobial resistance of coliforms and streptococci from broiler chickens. Poult. Sci. 61:1842-1852.
97. George, B. A., D. J. Fagerber, C. L. Quarles, J. M. Fenton, and G. A. McKinley. 1982. Effect of bambermycins on quality, prevalence, duration, and antimicrobial resistance of *Salmonella typhimurium* in experimentally infected broiler chickens. Am. J. Vet. Res. 43:299-303.
98. George, B. A., C. L. Quarles, and D. J. Fagerber. 1982. Virginiamycin effects on controlling necrotic enteritis infection in chickens. Poult. Sci. 61:447-450.
99. George, B. A., and D. J. Fagerber. 1984. Effect of bambermycins in vitro on plasmid mediated antimicrobial resistance. Am. J. Vet. Res. 45:2336-2341.
100. Gibot, S., G. Jeminet, J. Juillard, C. Gumila, M.-L. Ancelin, H. Vial, and A.-M. Derlot. 1999. Cationomycin and monensin partition between serum proteins and erythrocyte membrane: consequences for Na⁺ and K⁺ transport and antimicrobial activities. Arch. Biochem. Biophys. 363:361-372.
101. Goto, S., S. Miyazaki, and Y. Kaneko. 1992. In vitro activity of RP59500 against Gram-positive cocci. J. Antimicrob. Chemother. 30(Suppl. A):25-28.
102. Grayson, M. L., E. A. Grabsch, P. D. R. Johnson, D. Olden, M. Aberline, L. Hy, G. Hogg, M. Abbott, and P. G. Kerr. 1999. Outcome of a screening program for vancomycin-resistant enterococci in a hospital in Victoria. Med. J. Aust. 171:133-136.
103. Gumila, C., M.-L. Ancelin, G. Jeminet, A.-M. Delort, G. Miquel, and H. J. Vial. 1996. Differential in vitro activities of ionophore compounds against *Plasmodium falciparum* in mammalian cells. Antimicrob. Agents Chemother. 40:602-608.
104. Gumila, C., M.-L. Ancelin, A.-M. Delort, G. Jeminet, and H. J. Vial. 1997. Characterization of the potent in vitro and in vivo antimalarial activities of ionophore compounds. Antimicrob. Agents Chemother. 41:523-529.
105. Hall, C. C., J. D. Watkins, and N. H. Georgopapadakou. 1991. Comparison of the Tu elongation factors from *Staphylococcus aureus* and *Escherichia coli*: possible basis for elfamycin insensitivity. Antimicrob. Agents Chemother. 35:2366-2370.
106. Halvorson, D. A., C. Van Dijk, and P. Brown. 1982. Ionophore toxicity in turkey breeders. Avian Dis. 26:634-639.
107. Hammerum, A. M., L. B. Jensen, and F. M. Aarestrup. 1998. Detection of the *satA* genes and transferability of virginiamycin resistance in *Enterococcus faecium* from food-animals. FEMS Microbiol. Lett. 168:145-151.
108. Haney, M. E., and M. M. Hoehn. 1968. Monensin, a new biologically active compound. I. Discovery and isolation, p. 349-352. Antimicrob. agents Chemother. 1967.
109. Harel, Y. M., A. Bailone, and E. Bibi. 1999. Resistance to bacitracin as modulated by an *Escherichia coli* homologue of the bacitracin ABC transporter BcrC subunit from *Bacillus licheniformis*. J. Bacteriol. 181:6176-6178.
110. Haroche, J., J. Allignet, S. Aubert, A. E. van den Bogaard, and N. El Sohl. 2000. *satG*, Conferring resistance to streptogramin A, is widely distributed in *Enterococcus faecium* strains but not in staphylococci. Antimicrob. Agents Chemother. 44:190-191.
111. Haroche, J., J. Allignet, C. Buchrieser, and N. El Sohl. 2000. Characterization of a variant of *vga(A)* conferring resistance to streptogramin A and related compounds. Antimicrob. Agents Chemother. 44:2271-2275.
112. Hentschel, S., D. Kusch, and H.-J. Sinell. 1979. *Staphylococcus aureus* in poultry- biochemical characteristics, antibiotic resistance and phage pattern. Zentbl. Bakteriol. Mikrobiol. Hyg. I Abt. Orig. B 168:548-561.
113. Hinton, M. 1988. *Salmonella* colonization in young chickens given feed supplement with the growth promoting antibiotic avilamycin. J. Vet. Pharmacol. Ther. 11:269-275.
114. Huber, G., U. Schecht, H. L. Weidenmuller, J. Schmidt-Thomé, J. Duphorn, and R. Tschesche. 1966. Moenomycin, a new antibiotic. II. Characterization and chemistry, p. 737-742. Antimicrob. Agents Chemother. 1965.
115. Huber, G., and G. Neemann. 1968. Moenomycin, an inhibitor of cell wall synthesis. Biochem. Biophys. Res. Commun. 30:7-13.
116. Humpert, F., F. Lalande, R. l'Hospitalier, G. Salvat, and G. Bennejean. 1991. Effect of four antibiotic additives on the *Salmonella* contamination of chicks protected by an adult caecal flora. Avian Pathol. 20:577-584.
117. Huyke, M. M., F. Sahm, and M. S. Gilmore. 1998. Multiple-drug resistant enterococci: the nature of the problem and an agenda for the future. Emerg. Infect. Dis. 4:239-249.
118. Jacks, T. M., E. Frazier, F. R. Judith, G. Olsen. 1988. Effect of efrotomycin in feed in the quantity, duration and prevention of shedding and antibacterial susceptibility of *Salmonella typhimurium* in experimentally infected swine. Am. J. Vet. Res. 49:1832-1835.
119. Jensen, L. B., A. M. Hammerum, F. M. Aarestrup, A. R. van den Bogaard, and E. E. Stobberingh. 1998. Occurrence of *satA* and *vgaB* genes in strepto-

- gramin-resistant *Enterococcus faecium* isolates of animal and human origins in The Netherlands. *Antimicrob. Agents Chemother.* **42**:3330–3331.
120. **Jensen, L. B., A. M. Hammerum, and F. M. Aarestrup.** 2000. Linkage of *vat(E)* and *erm(B)* in streptogramin-resistant *Enterococcus faecium* isolates from Europe. *Antimicrob. Agents Chemother.* **44**:2231–2232.
 121. **Jones, R. N., and M. S. Barrett.** 1995. Antimicrobial activity of evernimycin (evernimicin), an oligosaccharide antimicrobial with a potent Gram-positive spectrum. *Clin. Microbiol. Infect.* **1**:35–43.
 122. **Jukes, T. H., and W. L. Williams.** 1953. Nutritional effects of antibiotics. *Pharmacol. Rev.* **5**:381–420.
 123. **Kaukas, A., M. Hinton, and A. H. Linton.** 1988. The effect of growth-promoting antibiotics on the faecal enterococci of healthy young chickens. *J. Appl. Bacteriol.* **64**:57–64.
 124. **Keshavarz, K., and L. B. McDougald.** 1982. Anticoccidial drugs: growth and performance depressing effects in young chickens. *Poult. Sci.* **61**:699–705.
 125. **Khan, A. A., T. R. Slifer, F. G. Araulo, and J. S. Remington.** 1999. Quinupristin/dalfopristin is active against *Toxoplasma gondii*. *Antimicrob. Agents Chemother.* **43**:2043–2045.
 126. **Klein, G., A. Pack, and G. Reuter.** 1998. Antibiotic resistance patterns of enterococci and the occurrence of vancomycin-resistant enterococci in raw minced beef and pork in Germany. *Appl. Environ. Microbiol.* **64**:1825–1830.
 127. **Kohlrausch, U., and J.-V. Höltje.** 1991. Analysis of murein and murein precursors during antibiotic-induced lysis of *Escherichia coli*. *J. Bacteriol.* **173**:3425–3431.
 128. **Komatsuzawa, H., J. Suzuki, M. Sugai, Y. Miyake, and H. Suginaka.** 1994. Effect of combination of oxacillin and non- β -lactam antibiotics on methicillin-resistant *Staphylococcus aureus*. *J. Antimicrob. Chemother.* **33**:1155–1163.
 129. **Kondo, F.** 1988. In vitro lecithinase activity and sensitivity to 22 antimicrobial agents of *Clostridium perfringens* isolated from necrotic enteritis of broiler chickens. *Res. Vet. Sci.* **45**:337–340.
 130. **Kyriakis, S. C.** 1989. The effect of avilamycin in the control of stress induced post-weaning diarrhea in piglets. *J. Vet. Pharmacol. Ther.* **12**:296–301.
 131. **Kyriakis, S. C.** 1989. The effect of monensin against swine dysentery. *Br. Vet. J.* **145**:373–377.
 132. Reference deleted.
 133. **Kyriakis, S. C., K. Sarris, S. K. Kritas, K. Saoulidis, A. C. Tsinas, and V. K. Tsiloyiannis.** 1995. The effect of salinomycin on the control of *Clostridium perfringens* type-A infection in growing pigs. *J. Vet. Med. Ser. B* **42**:355–359.
 134. **Kyriakis, S. C., A. Tsinas, S. Lekkas, K. Sarris, and E. Bourtzzi-Hatzopoulou.** 1996. Clinical evaluation of in-feed zinc bacitracin for the control of porcine intestinal adenomatosis for growing/fattening pigs. *Vet. Rec.* **138**:489–492.
 135. **Lai, C. J., and B. Weisblum.** 1971. Altered methylation of ribosomal RNA in an erythromycin-resistant strain of *Staphylococcus aureus*. *Proc. Natl. Acad. Sci. USA* **68**:856–860.
 136. **Lämmle, C., N. Cirak, and J. Smola.** 1998. Studies on biochemical, serological and further characteristics of *Streptococcus porcinus*. *J. Vet. Med. Ser. B* **45**:235–243.
 137. **Landini, P., M. Bandera, B. P. Goldstein, F. Ripamonti, A., Soffientini, K. Islam, and M. Denaro.** 1992. Inhibition of bacterial protein synthesis by elongation-factor-Tu-binding antibiotics MDL 62,879 and efrotomycin. *Biochem. J.* **283**:649–652.
 138. **Landini, P., M. Bandera, A. Soffientini, and B. P. Goldstein.** 1993. Sensitivity of elongation factor Tu (EF-Tu) from different bacterial species to the antibiotics efrotomycin, pulvomycin, and MDL 62879. *J. Gen. Microbiol.* **139**:769–774.
 139. **Lebek, G.** 1972. Die Wirkung von Flavomycin auf episomal resistente Keime. *Zentbl. Veterinärmed. Reihe B* **19**:532–539.
 140. **Leclercq, R., and P. Courvalin.** 1991. Bacterial resistance to macrolide, lincosamide, and streptogramin antibiotics by target modification. *Antimicrob. Agents Chemother.* **35**:1267–1272.
 141. **Leclercq, R., and P. Courvalin.** 1991. Intrinsic and unusual resistance to macrolide, lincosamide, and streptogramin antibiotics in bacteria. *Antimicrob. Agents Chemother.* **35**:1273–1276.
 142. **Leclercq, R., L. Nantes, C.-J. Soussy, and J. Duval.** 1992. Activity of RP 59500, a new parenteral semisynthetic streptogramin, against staphylococci with various mechanisms of resistance to macrolide-lincosamide-streptogramin antibiotics. *J. Antimicrob. Chemother.* **30**(Suppl. A):67–75.
 143. **Liassine, N., J. Allignet, A. Morvan, S. Aubert, and N. El Solh.** 1997. Multiplicity of the genes and plasmids conferring resistance to pristinamycin in staphylococci selected in an Algerian hospital. *Zentbl. Bakteriologie.* **286**:389–399.
 144. **Lina, G., A. Quaglia, M.-E. Reverdy, R. Leclercq, F. Vandenesch, and J. Etienne.** 1999. Distribution of genes encoding resistance to macrolides, lincosamides, and streptogramins among staphylococci. *Antimicrob. Agents Chemother.* **43**:1062–1066.
 145. **Linden, P. K., A. W. Pasculle, D. McDevitt, and D. J. Kramer.** 1997. Effect of quinupristin/dalfopristin on the outcome of vancomycin-resistant *Enterococcus faecium* bacteraemia: comparison with a control cohort. *J. Antimicrob. Chemother.* **39**(Suppl. A):145–151.
 146. **Lindsay, D. S., and B. L. Blagburn.** 1995. Antiprotozoan drugs. p. 969–983. *In* H. R. Adams (ed.), *Veterinary pharmacology and therapeutics*. Iowa State University Press, Ames.
 147. **Linton, K. J., H. N. Cooper, I. S. Hunter, and P. F. Leadlay.** 1994. An ABC transporter system for *Streptomyces longisporoflavus* confers resistance to the polyether-ionophore antibiotic tetronasin. *Mol. Microbiol.* **11**:777–785.
 148. **Magnussen, J. D., J. E. Dalidowicz, T. D. Thomson, and A. L. Donoho.** 1991. Tissue residues and metabolism of avilamycin in swine and rats. *J. Agric. Food Chem.* **39**:306–310.
 149. **Mann, P. A., L. Xiong, A. S. Mankin, A. S. Chau, C. A. Mendrick, D. J. Najarian, C. A. Cramer, D. Loebenberg, E. Coates, N. J. Murgolo, F. M. Aarestrup, R. V. Goering, T. A. Black, R. S. Hare, and P. M. McNicholas.** 2001. EmtA, a rRNA methyltransferase conferring high-level evernimicin resistance. *Mol. Microbiol.* **41**:1349–1356.
 150. **Manning, J. G., B. M. Hargis, A. Hinton, Jr., D. E. Corrier, J. R. DeLoach, and C. R. Greger.** 1994. Effect of selected antibiotics and anticoccidials on salmonella enteritidis cecal colonization and organ invasion in leghorn chicks. *Avian Dis.* **38**:256–261.
 151. **Marounek, M., and V. Rada.** 1995. Susceptibility of poultry lactobacilli to ionophore antibiotics. *J. Vet. Med. Ser. B* **42**:193–196.
 152. **McNicholas, P. M., D. J. Najarian, P. A. Mann, D. Hesk, R. S. Hare, K. J. Shaw, and T. A. Black.** 2000. Evernimycin binds exclusively to the 50S ribosomal subunit and inhibits translation in cell-free systems derived from both gram-positive and gram-negative bacteria. *Antimicrob. Agents Chemother.* **44**:1121–1126.
 153. **Mertz, J. L., J. S. Peloso, B. J. Barker, G. E. Babitt, J. L. Occolowitz, V. L. Simson, and R. M. Kline.** 1986. Isolation and structural identification of nine avilamycins. *J. Antibiot.* **39**:877–887.
 154. **Mevis, D. J., K. T. Veldman, A. van der Giessen, and W. J. van Leeuwen.** 2000. Eerste resultaten van de monitoring van antibioticum-resistentie in Nederland. *Tijdschr. Diergen.* **125**:143–146.
 155. **Miele, A., B. P. Goldstein, M. Bandera, C. Jarvis, A. Resconi, and R. J. Williams.** 1994. Differential susceptibilities of enterococcal species to elfamycin antibiotics. *J. Clin. Microbiol.* **32**:2016–2018.
 156. **Miller, R. E., W. J. Boever, R. E. Junge, L. P. Thornburg, and M. F. Raisbeck.** 1990. Acute monensin toxicosis in stone sheep (*Ovis dalli stonei*), blesbok (*Damaliscus dorcus*), and a Bactrian camel (*Camelus bactrianus*). *J. Am. Vet. Med. Assoc.* **196**:131–134.
 157. **Moazed, D., and H. F. Noller.** 1987. Chloramphenicol, erythromycin, carbomycin and veramycin B protect overlapping sites in the peptidyl transferase region of 23S ribosomal RNA. *Biochemie* **69**:879–884.
 158. **Moellering, R. C.** 1999. Quinupristin/dalfopristin: therapeutic potential for vancomycin-resistant enterococcal infections. *J. Antimicrob. Chemother.* **44**(Topic A):25–30.
 159. **Moellering, R. C., P. K. Linden, J. Reinhardt, A. E. Blumberg, F. Bompert, and G. H. Talbot, for the Synercid Emergency-Use Study Group.** 1999. The efficacy and safety of quinupristin/dalfopristin for the treatment of infections caused by vancomycin-resistant *Enterococcus faecium*. *J. Antimicrob. Chemother.* **44**:251–261.
 160. **Mulder, R. W. A. W., and M. C. Van der Hulst-Van Arkel.** 1976. Residuen van antibiotica in organen en pluimveevlees. *Tijdschr. Diergeneesk.* **101**:1194–1198.
 161. **Mutton, K. J., and J. H. Andrew.** 1983. In vitro activity of pristinamycin against methicillin-resistant *Staphylococcus aureus*. *Chemotherapy* **29**:218–224.
 162. **Muylle, E., C. Vandenhende, W. Oyaert, H. Thoonen, and K. Vlaeminck.** 1981. Delayed monensin sodium toxicity in horses. *Equine Vet. J.* **13**:107–108.
 163. **Nakashio, S., H. Iwasawa, F. Y. Dun, K. Kanemitsu, and J. Shimada.** 1995. Evernimycin, a new oligosaccharide antibiotic: its antimicrobial activity, post-antibiotic effect and synergistic bactericidal activity. *Drugs Exp. Clin. Res.* **11**:7–16.
 164. **Nurmi, E., and M. Rantala.** 1974. The influence of zinc bacitracin on the colonization of *Salmonella infantis* in the intestine of broiler chickens. *Res. Vet. Sci.* **17**:24–27.
 165. **O'Donovan, C. A., P. Fan-Havard, F. T. Tecson-Tumang, S. M. Smith, and R. H. Eng.** 1994. Enteric eradication of vancomycin-resistant *Enterococcus faecium* with oral bacitracin. *Diagn. Microbiol. Infect. Dis.* **18**:105–109.
 166. **O'Grady, F., and D. Greenwood.** 1997. Cyclic peptides, p. 336–343. *In* F. O'Grady, H. P. Lambert, R. Finch, and D. Greenwood (ed.), *Antibiotic and chemotherapy: anti-infective agents and their use in therapy*, 7th ed. Churchill Livingstone, Inc., New York, N.Y.
 167. **Paik, J., I. Kern, R. Lurz, and R. Hakenbeck.** 1999. Mutational analysis of the *Streptococcus pneumoniae* bimodular class A penicillin-binding proteins. *J. Bacteriol.* **181**:3852–3856.
 168. **Parmeggiani, A., and G. W. M. Swart.** 1985. Mechanism of action of kirromycin-like antibiotics. *Annu. Rev. Microbiol.* **39**:757–757.
 169. **Péchère, J. C.** 1999. Current and future management of infections due to methicillin-resistant staphylococci infections: the role of quinupristin/dalfopristin. *J. Antimicrob. Chemother.* **44**(Topic A):11–18.

170. Plumlee, K. H., B. Johnson, and F. D. Galey. 1995. Acute salinomycin toxicosis of pigs. *J. Vet. Diagn. Investig.* 7:419-420.
171. Podlesek, Z., A. Comino, B. Herzog-Velikonja, D. Zgur-Bertok, R. Komel, and M. Grabnar. 1995. *Bacillus licheniformis* bacitracin-resistance ABS transporter: relationship to mammalian multidrug resistance. *Mol. Microbiol.* 16:969-976.
172. Pollock, T. J., L. Thorne, M. Yamazaki, M. J. Mikolajczak, and R. W. Armentrout. 1994. Mechanism of bacitracin resistance in Gram-negative bacteria that synthesize exopolysaccharides. *J. Bacteriol.* 176:93-98.
173. Portillo A., F. Ruiz-Larrea, M. Zarazaga, A. Alonso, J. L. Martinez, and C. Torres. 2000. Macrolide resistance genes in *Enterococcus* species. *Antimicrob. Agents Chemother.* 44:967-971.
174. Prescott, J. F. 1979. The prevention of experimentally induced necrotic enteritis by avoparcin. *Avian Dis.* 24:1072-1074.
175. Prescott, J. F., and J. D. Baggot. 1993. Growth promotion and feed antibiotics, p. 562-568. In J. F. Prescott, and J. D. Baggot (ed.), *Antimicrobial therapy in veterinary medicine*, 2nd ed. Iowa State University Press, Ames.
176. Pressman, B. C., and M. Fahim. 1982. Pharmacology and toxicology of the monovalent carboxylic ionophores. *Annu. Rev. Pharmacol. Toxicol.* 22:465-490.
177. Pressman, B. C. 1976. Biological applications of ionophores. *Annu. Rev. Biochem.* 45:501-530.
178. Prohaszka, L., E. Hadju, E. Dworschalk, and T. Rozsnyai. 1987. Growth depression in broiler chickens caused by incompatibility of feed ingredients. *Acta Vet. Hung.* 35:349-358.
179. Reece, R. L., D. A. Barr, W. M. Forsyth, and P. C. Scott. 1985. Investigation of toxicity episodes involving chemotherapeutic agents in Victorian poultry and pigeons. *Avian Dis.* 29:1239-1251.
180. Rende-Fournier, R., R. Leclercq, M. Galimard, J. Duval, and P. Courvalin. 1993. Identification of the *satA* gene encoding a streptogramin A acetyltransferase in *Enterococcus faecium* BM4145. *Antimicrob. Agents Chemother.* 37:2119-2125.
181. Renoux, G., and Y. Michel-Briand. 1962. Détermination de la sensibilité de *Staphylococcus pyogenes* au 7 293 RP (pristinamycine) par la méthode des disques. *Ann. Inst. Pasteur* 102:488-492.
182. Riedl, S., K. Ohlsen, G. Werner, W. Witte, and J. Hacker. 2000. Impact of flavophospholipol and vancomycin on conjugational transfer of vancomycin resistance plasmids. *Antimicrob. Agents Chemother.* 44:3189-3192.
183. Roberts, M. C., J. Sutcliffe, P. Courvalin, L. B. Jensen, J. Rood, and H. Seppala. 1999. Nomenclature for macrolide and macrolide-lincosamide-streptogramin B resistance determinants. *Antimicrob. Agents Chemother.* 43:2823-2830.
184. Ross, J. L., E. A. Eady, J. H. Cove, W. J. Cunliffe, S. Baumberg, and J. C. Wootton. 1990. Inducible erythromycin resistance in staphylococci is encoded by a member of the ATP-binding transport super-gene family. *Mol. Microbiol.* 4:1207-1214.
185. Rubinstein, E., and F. Bompard. 1999. Activity of quinupristin/dalfopristin against Gram-positive bacteria: clinical applications and therapeutic potential. *J. Antimicrob. Chemother.* 39(Suppl. A):139-143.
186. Rubinstein, E., P. Prokocimer, and G. H. Talbot. 1999. Safety and tolerance of quinupristin/dalfopristin: administration guidelines. *J. Antimicrob. Chemother.* 44(Topic A):37-46.
187. Sambeth, W., G. Neseaman, F. Bauer, and G. Dost. 1969. Investigations of the excretion and retention of flavomycin, p. 133-139. *Flavomycin Symposium*.
188. Schmitz, F.-J., J. Verhoef, A. C. Fluit, and The Sentry Participants Group. 1999. Prevalence of resistance to MLS antibiotics in 20 European university hospitals participating in the European SENTRY surveillance programme. *J. Antimicrob. Chemother.* 43:783-792.
189. Schouten, M. A., A. Voss, J. A. A. Hoogkamp-Korstanje, and The European VRE Study Group. 1999. Antimicrobial susceptibility patterns of enterococci causing infections in Europe. *Antimicrob. Agents Chemother.* 43:2542-2546.
190. Shiffer, G., and J.-V. Høltje. 1999. Cloning and characterization of PBP 1C, a third member of multimodular class A penicillin-binding proteins of *Escherichia coli*. *J. Biol. Chem.* 274:32031-32039.
191. Shumard, R. F., and M. E. Callender. 1968. Monensin, a new biologically active compound. VI. Anticoccidial activity, p. 369-377. *Antimicrob. Agents Chemother.* 1967.
192. Shlosberg, A., S. Perl, A. Harmelin, V. Hanji, M. Bellaiche, E. Bogin, R. Cohen, O. Markusfeld-Nir, N. Shpigel, Z. Eisenberg, A. Brosh, Z. Holzer, and Y. Aharoni. 1997. Acute maduramicin toxicity in calves. *Vet. Rec.* 140:643-646.
193. Siewert, G., and J. L. Strominger. 1967. Bacitracin: an inhibitor of the dephosphorylation of lipid pyrophosphate, an intermediate in biosynthesis of the peptidoglycan of bacterial cell walls. *Proc. Natl. Acad. Sci. USA* 57:767-773.
194. Sippel, K., B. Dülffer-Schneitzer, and C. Lämmler. 1995. Characteristic properties of streptococci of serological group. *L. J. Vet. Med. Ser. B* 42:42-50.
195. Smith, H. W., and J. F. Tucker. 1975. The effect of feeding diets containing permitted antibiotics on the fecal excretion of *Salmonella typhimurium* by experimentally infected chickens. *J. Hyg.* 75:293-301.
196. Smith, I., and P. Paress. 1978. Genetic and biochemical characterization of kirromycin resistance mutations in *Bacillus subtilis*. *J. Bacteriol.* 35:1107-1117.
197. Soltani, M., D. Beighton, J. Philpott-Howard, and N. Woodford. 2000. Mechanism of resistance to quinupristin-dalfopristin among isolates of *Enterococcus faecium* from animals, raw meat, and hospital patients in Western Europe. *Antimicrob. Agents Chemother.* 44:433-436.
198. Soltani, M., D. Beighton, J. Philpott-Howard, and N. Woodford. 2001. Identification of *vat(E-3)*, a novel gene encoding resistance to quinupristin-dalfopristin in a strain of *Enterococcus faecium* from a hospital patient in the United Kingdom. *Antimicrob. Agents Chemother.* 45:645-646.
199. Spring, W. G. 1978. Der einfluss von Flavomycin auf die Salmonelleninfektion und Antibiotikaresistenz bei Kälbern. *Tierärztl. Umschau* 33:467-470.
200. Stipkovits, L., T. Kobulej, and Z. Varga. 1985. Efficacy of lasalocid against *Mycoplasma*. *Vet. Bull.* 55:723.
201. Stipkovits, L., T. Kobulej, Z. Varga, and S. Juhasz. 1987. In vitro testing of the anti-mycoplasma effect of some anti-coccidial drugs. *Vet. Microbiol.* 15:65-70.
202. Stone, K. J., and J. L. Strominger. 1971. Mechanism of action of bacitracin: complexation with metal ion and C₅₅-isoprenyl pyrophosphate. *Proc. Natl. Acad. Sci. USA* 68:3223-3227.
203. Storm, D. R. 1974. Mechanism of bacitracin action: a specific lipid-peptide interaction. *Ann. N. Y. Acad. Sci.* 235:387-398.
204. Stratton, C. W. 2000. Quinupristin/dalfopristin: the first parenteral streptogramin. *Antimicrob. Infect. Dis. Newsl.* 18:41-48.
205. Stuart, J. G., and J. J. Ferretti. 1978. Genetic analysis of antibiotic resistance in *Streptococcus pyogenes*. *J. Bacteriol.* 133:852-859.
206. Stutz, M. W., S. L. Johnson, and F. R. Judith. 1983. Effects of diet and bacitracin on growth, feed efficiency, and populations of *Clostridium perfringens* in the intestine of broiler chicks. *Poult. Sci.* 62:1619-1625.
207. Stutz, M. W., and G. C. Lawton. 1984. Effects of diet and antimicrobials on growth, feed efficiency, intestinal *Clostridium perfringens*, and ileal weight of broiler chicks. *Poult. Sci.* 63:2036-2042.
208. Stutz, M. W., S. L. Johnson, F. R. Judith, and B. M. Miller. 1983. In vitro and in vivo evaluations of the antibiotic efrotomycin. *Poult. Sci.* 62:1612-1618.
209. Subramaniam-Niehaus, B., T. Schneider, J. W. Metzger, and W. Wohlleben. 1997. Isolation and analysis of moenomycin and its biosynthetic intermediates from *Streptomyces ghanaensis* (ATCC 14672) wildtype and selected mutants. *Z. Naturforsch.* 52:217-226.
210. Suter, W., A. Rosselet, and F. Knüsel. 1978. Mode of action of quindoxin and substituted quinoxaline-di-N-oxides on *Escherichia coli*. *Antimicrob. Agents Chemother.* 13:770-783.
211. Thal, L. A., and M. J. Zervos. 1999. Occurrence and epidemiology of resistance to virginiamycin and streptogramins. *J. Antimicrob. Chemother.* 43:171-176.
212. Torres, J. S., L. B. Narvaez, A. V. Oliveros, and E. A. Gonzalez. 1985. Efecto de la bacitracina zinc sobre el crecimiento y microflora intestinales de pollos de engorda. *Vet. Mex.* 16:257-260.
213. Umemura, T., H. Nakamura, M. Goryo, and C. Itakura. 1984. Histopathology of monensin-tiamulin myopathy in broiler chickens. *Avian Pathol.* 13:459-468.
214. Uttley, A. H., C. H. Collins, J. Naidoo, and R. C. George. 1988. Vancomycin-resistant enterococci. *Lancet* i:57-58.
215. Vahjen, W., K. Gollnisch, O. Simon, and E. Schulz. 2000. Development of a semiquantitative PCR assay for the detection of the *Clostridium perfringens* type C beta toxin gene in purified nucleic acid extracts from the intestinal tract of pigs. *J. Agric. Sci.* 134:77-87.
216. van de Klundert, J. A., E. den Turk, A. H. Borman, P. H. van der Meide, and L. Bosch. 1977. Isolation and characterization of mocimycin-resistant mutant of *Escherichia coli* with an altered elongation factor EF-Tu. *FEBS Lett.* 81:303-307.
217. van den Bogaard, A. E., P. Mertens, N. H. London, and E. E. Stobberingh. 1997. High prevalence of colonization with vancomycin- and pristinamycin-resistant enterococci in healthy humans and pigs in The Netherlands: is the addition of antibiotics to animal feeds to blame? *J. Antimicrob. Chemother.* 40:454-456.
218. van den Bogaard, A. E. J. M., N. H. London, and E. E. Stobberingh. 1997. Antimicrobial resistance in pig fecal samples from The Netherlands (five abattoirs) and Sweden. *J. Antimicrob. Chemother.* 45:663-671.
219. van den Bogaard, A. E., M. Hazen, M. Hoyer, P. Oostenbach, and E. E. Stobberingh. 2002. Effects of flavophospholipol on resistance in fecal *Escherichia coli* and enterococci from fattening pigs. *Antimicrob. Agents Chemother.* 46:110-118.
220. Vanderwel, D., and E. E. Ishiguro. 1984. Properties of cell wall peptidoglycan synthesized by amino acid-deprived relA mutants of *Escherichia coli*. *Can. J. Microbiol.* 30:1239-1246.
221. Van Heienoort, Y., M. Derrien, and J. Van Heijenoort. 1978. Polymerization by transglycolation in the biosynthesis of the peptidoglycan of *Escherichia coli* K12 and its inhibition by antibiotics. *FEBS Lett.* 89:141-144.

222. Van Heijenoort, Y., M. Leduc, H. Singer, and J. Van Heijenoort. 1987. Effects of moenomycin on *Escherichia coli*. *J. Gen. Microbiol.* **133**:667–674.
223. Vicarini, H., A. Rosato, and R. Leclercq. 1997. Analysis of regulatory region of *ermAM* genes in streptococci and enterococci highly resistant to macrolides and lincosamides, p. 495–498. In T. Horaud, A. Bouvet, R. Leclercq, H. de Montclos, and D. Sicard (ed.), *Streptococci and the host*. Plenum Press, Inc., New York, N.Y.
224. Vissiennon, T., H. Kröger, T. Köhler, and R. Kliche. 2000. Effect of avilamycin, tylosin and ionophore anticoccidials on *Clostridium perfringens* enterotoxaemia in chickens. *Berl. Munch. Tierarztl. Wochenschr.* **113**:9–13.
225. Vollmer, W., M. von Rechenberg, and J.-V. Höltje. 2000. Demonstration of molecular interactions between the murein polymerase PBP 1b, the lytic transglycosylase MltA, and the scaffolding protein MipA of *Escherichia coli*. *J. Biol. Chem.* **274**:6726–6734.
226. Von Kaemmerer, K., and M. Kietzmann. 1980. Untersuchungen über pharmakodynamische Effekte von Zinkbacitracin im nutritiven Dosierungsbereich. *Berl. Munch. Tierarztl. Wochenschr.* **93**:478–481.
227. Von Wendt, M., S. Büsing, and W. Bollwahn. 1997. Zur Toxizität der Kombination von Salinomycin und Tiamutilin beim Schwein. *Dtsch. Tierarztl. Wochenschr.* **104**:405–410.
228. Watanabe, K., J. Watanabe, S. Kuramitsu, and H. B. Maruyama. 1981. Comparison of the activity of ionophores with other antibacterial agents against anaerobes. *Antimicrob. Agents Chemother.* **19**:519–525.
229. Wallhauser, K. H., G. Nesemann, P. Prave, and A. Steigler. 1966. Moenomycin, a new antibiotic. I. Fermentation and isolation, p. 734–736. *Antimicrob. Agents Chemother.* **1965**.
230. Wasielewski, E., R. Mushawek, and E. Schütze. 1966. Moenomycin, a new antibiotic. III. Biological properties, p. 743–748. *Antimicrob. Agents Chemother.* **1965**.
231. Watkins, K. L., T. R. Shyrock, R. N. Dearth, and Y. M. Saif. 1997. In vitro antimicrobial susceptibility of *Clostridium perfringens* from commercial turkey and broiler chicken origin. *Vet. Microbiol.* **54**:195–200.
232. Wax, R., W. Maiese, R. Weston, and J. Birnbaum. 1976. Efrptomycin, a new antibiotic from *Streptomyces lacamdurans*. *J. Antibiot.* **29**:670–673.
233. Weinstein, M. J., G. M. Leudemann, E. M. Oden, and G. H. Wagman. 1965. Everninomycin, a new antibiotic complex from *Micromonospora carbonacea*, p. 24–32. *Antimicrob. Agents Chemother.* **1964**.
234. Weinstein, M. R., H. Dedier, J. Brunton, L. Campell, and J. M. Conly. 1999. Lack of efficacy of oral bacitracin plus doxycycline for the eradication of stool colonization with vancomycin-resistant *Enterococcus faecium*. *Clin. Infect. Dis.* **29**:361–366.
235. Weisblum, B. 1985. Inducible resistance to macrolides, lincosamides and streptogramin type B antibiotics: the resistance phenotype, its biological diversity, and structural elements that regulate expression—a review. *J. Antimicrob. Chemother.* **16**(Suppl. A):63–90.
236. Weisblum, B. 1995. Insights into erythromycin action from studies of its activity as inducer of resistance. *Antimicrob. Agents Chemother.* **39**:797–805.
237. Weitnauer, G., S. Gaisser, A. Trefzer, S. Stockert, L. Westrich, L. M. Quiros, C. Mendez, J. A. Salas, and A. Bechthold. 2001. An ATP-binding cassette transporter and two rRNA methyltransferases are involved in resistance to avilamycin in the producer organism *Streptomyces viridochromogenes* Tü57. *Antimicrob. Agents Chemother.* **45**:690–695.
238. Welton, L. A., L. A. Thal, M. B. Perri, S. Donabedian, J. McMahon, J. W. Chow, and M. J. Zervos. 1998. Antimicrobial resistance in enterococci isolated from turkey flocks fed virginiamycin. *Antimicrob. Agents Chemother.* **42**:705–708.
239. Werckenthin, A., S. Schwarz, and H. Westh. 1999. Structural alterations in the translational attenuator of constitutively expressed *ermC* genes. *Antimicrob. Agents Chemother.* **43**:1681–1685.
240. Werner, G., and W. Witte. 1999. Characterization of a new enterococcal gene, *satG*, encoding a putative acetyltransferase conferring resistance to streptogramin A compounds. *Antimicrob. Agents Chemother.* **43**:1813–1814.
241. Westley, J. W. 1982. Notation and classification, p. 1–20. In J. W. Westley (ed.), *Polyether antibiotics: naturally occurring acid ionophores*, vol. 1. Biology. Marcel Dekker, Inc., New York, N.Y.
242. Westley, J. W. 1983. Chemical transformations of polyether antibiotics, p. 51–87. In J. W. Westley (ed.), *Polyether antibiotics: naturally occurring acid ionophores*, vol. 2. Chemistry. Marcel Dekker, Inc., New York, N.Y.
243. Wicker, D. L., W. N. Isgrigg, J. H. Trammel, and R. B. Davis. 1977. The control and prevention of necrotic enteritis in broilers with zinc-bacitracin. *Poult. Sci.* **56**:1229–1231.
244. Williamson, R., L. Gutmann, T. Horaud, F. Delbos, and J. F. Acar. 1986. Use of penicillin-binding proteins for the identification of enterococci. *J. Gen. Microbiol.* **132**:1929–1937.
245. Wolf, H. 1973. Avilamycin, an inhibitor of the 30S ribosomal subunit function. *FEBS Lett.* **36**:181–186.
246. Wolf, H., G. Chinali, and A. Parmeggiani. 1977. Mechanism of the inhibition of protein synthesis by kirromycin. *Eur. J. Biochem.* **75**:67–75.
247. Wondrack, L., M. Massa, B. V. Yang, and J. Sutcliffe. 1996. Clinical strain of *Staphylococcus aureus* inactivates and causes efflux of macrolides. *Antimicrob. Agents Chemother.* **40**:992–998.