

Zeitschrift: Mitteilungen aus Lebensmitteluntersuchungen und Hygiene = Travaux de chimie alimentaire et d'hygiène

Herausgeber: Bundesamt für Gesundheit

Band: 92 (2001)

Heft: 1

Artikel: Antibiotic resistance epidemiology : links between antibiotic use in food animals and resistance in human bacteria

Autor: Bogaard, Anthony E. van den / Stobberingh, Ellen E.

DOI: <https://doi.org/10.5169/seals-981898>

Nutzungsbedingungen

Die ETH-Bibliothek ist die Anbieterin der digitalisierten Zeitschriften auf E-Periodica. Sie besitzt keine Urheberrechte an den Zeitschriften und ist nicht verantwortlich für deren Inhalte. Die Rechte liegen in der Regel bei den Herausgebern beziehungsweise den externen Rechteinhabern. Das Veröffentlichen von Bildern in Print- und Online-Publikationen sowie auf Social Media-Kanälen oder Webseiten ist nur mit vorheriger Genehmigung der Rechteinhaber erlaubt. [Mehr erfahren](#)

Conditions d'utilisation

L'ETH Library est le fournisseur des revues numérisées. Elle ne détient aucun droit d'auteur sur les revues et n'est pas responsable de leur contenu. En règle générale, les droits sont détenus par les éditeurs ou les détenteurs de droits externes. La reproduction d'images dans des publications imprimées ou en ligne ainsi que sur des canaux de médias sociaux ou des sites web n'est autorisée qu'avec l'accord préalable des détenteurs des droits. [En savoir plus](#)

Terms of use

The ETH Library is the provider of the digitised journals. It does not own any copyrights to the journals and is not responsible for their content. The rights usually lie with the publishers or the external rights holders. Publishing images in print and online publications, as well as on social media channels or websites, is only permitted with the prior consent of the rights holders. [Find out more](#)

Download PDF: 30.04.2026

ETH-Bibliothek Zürich, E-Periodica, <https://www.e-periodica.ch>

Antibiotic Resistance Epidemiology: Links between Antibiotic Use in Food Animals and Resistance in Human Bacteria*

Anthony E. van den Bogaard and Ellen E. Stobberingh, University Maastricht Department of Medical Microbiology, Maastricht

Introduction

Approximately 50% of all antibacterial agents used yearly in the European Union (EU) are given to animals (1). These antibiotics are not only used (on veterinary indication) for therapy and the prevention of bacterial infections, but they are also added continuously to animal feeds to promote growth, to increase feed efficacy, and to decrease waste production. The antibiotics used for this purpose are commonly called feed savers, performance enhancers, or antimicrobial growth promoters (AMGP). In Europe, approximately 30% of all antibiotics used in animals are used as AMGP, but large differences between the EU member states exist. Since the recommendations of the Swann report (1) in 1969 have been followed by most EU member states, molecules that are used for therapy in humans and/or animals are not allowed to be used as AMGP. However, many of the AMGP that are used today in the EU are analogues of, and show cross-resistance with, therapeutic antibiotics. AMGP are mainly active against Gram-positive bacteria (2–3) (table I) (4), with the exception of carbadox and olaquinox, which are mainly active against Gram-negatives (5). Approximately 90% of all antibiotics used for veterinary purposes are given orally to food animals like poultry, pigs and calves. In these cases, the antibiotics are mostly mixed in the feed, but sometimes they are poured over the feed or dissolved in the drinking water or milk. In the Netherlands, AMGP are included in nearly all feeds for pigs, broilers, and veal calves. The amount of antibiotics used as AMGP is of the same size order as for veterinary purposes; 250 vs. 300 tons of active drug (2). In other countries, like the UK for example, the veterinary use is more than three times as high as the use for growth promotion.

* Presented at the 33rd Symposium of the Swiss Society of Food Hygiene, Zurich, 16 November 2000

Table 1

Normal susceptibility ranges of clostridia and enterococci for some AMGP compared to permitted levels in feed for performance enhancement (modified from (2) and (3))

<i>Antibacterial substance</i>	<i>Range of Minimum Inhibitory Concentrations (MIC in mg/l)</i>		<i>Dosage used for growth enhancement (mg/Kg feed)</i>
	<i>Clostridia</i>	<i>Enterococci</i>	
Avilamycin (evernimomycin)	< 0.25–0.5	Not available	2.5–40
Avoparcin (glycopeptide)	0.5–2	1–2	5–40
Bacitracin (polypeptides)	1–4	0.5–16	5–100
Flavophospholipol (bambermycins)	< 1–8	0.25–4	1–25
Monensin (polyether)	0.5–4	1–2	10–40
Spiramycin (macrolide)	0.25–8	0.5–4	5–80
Tylosin (macrolide)	< 1	1–4	4–40
Virginiamycin (pristinamycin)	0.25–1	0.25–8	5–80

Resistance

Many retrospective and prospective studies have been performed concerning the emergence and selection of resistance in bacteria by the use of antibiotics. Despite large differences in methodology, most results show after the introduction of antibiotic into veterinary practice, resistance in pathogenic bacteria and/or in faecal flora increases, like in human medicine. Some bacteria, however, like most *Enterobacteriaceae*, staphylococci and *Pasteurella* spp., become more readily resistant to certain antibiotics than others do, such as *Clostridium* spp. and streptococci, which are still fully susceptible to penicillin-G.

The literature on resistance against AMGP is very limited as most of these molecules are not used for therapy and therefore susceptibility testing is not regularly performed. *Linton et al.* (6) found a significant increase in the prevalence of resistance against tylosin and bacitracin in faecal enterococci of pigs and poultry that had been fed these substances. Virginiamycin usage, however, did not result in an increase in resistance in this study. After the introduction of olaquinox in 1982 on farms using olaquinox as an AMGP, the prevalence of resistance in faecal *Escherichia coli* in pigs increased in three years from 0.004 to 6 %, whereas on farms not using olaquinox the prevalence of resistance increased as well, but to a significantly lesser degree, suggesting dissemination of resistant clones (7).

Ohmae et al. (8–9) noticed an increase of resistance against carbadox in faecal *E. coli* isolates of pigs after its introduction as an AMGP. All resistant isolates from six farms that fed carbadox continuously to pigs either as AMGP or for the prevention of swine dysentery, carried the same transferable plasmid conferring carbadox resistance. Carbadox is not used in poultry and no carbadox resistance was found in *E. coli* isolates from poultry in the same region. *Mills and Kelly* (10) also reported, after the introduction of carbadox, an increase in resistance in *E. coli* isolates from 37 to 61 %. Carbadox, however, was not only used as an AMGP, but also for the prevention of swine dysentery and as therapy for salmonellosis.

Interest in the selection of resistance by AMGP increased after the emergence of vancomycin resistance enterococci (VRE) in human infections. It was soon recognised that avoparcin, like vancomycin, a glycopeptide and until recently commonly used as AMGP in most EU member states, selects for VRE in the intestinal flora of animals (11). In countries where avoparcin was used as an AMGP, VRE were not only found in food animals fed avoparcin, but also in the faecal flora of healthy humans and in pet animals (5, 12–15) (table II). Furthermore, resistance against MLS antibiotics like erythromycin and pristinamycins (quinupristin-dalfopristin) is quite common in enterococci from animals fed related antibiotics as AMGP, like tylosin (a macrolide) or virginiamycin (a pristinamycin) (15). Similar figures have been found in other European countries such as Denmark (16), where in 1995 a prevalence of resistance was found in enterococci from pigs and poultry against vancomycin (21 % and 56 %), erythromycin (91 % and 59 %), and quinupristin-dalfopristin (53 % and 37 %). In Finland, however, where tylosin is not used as an

Table 2

Prevalence of vancomycin, erythromycin, and pristiniamycin resistant enterococci in the faecal flora of healthy animals and humans in the Netherlands

Population	n	Prevalence of resistance		
		Vancomycin/ VanA	Erythromycin	Quinupristin- dalfopristin*
Veal calves	539	92	—	—
Broilers	51	80	94	98
Turkeys	47	50	—	—
Pigs	282	34	84	75
Dogs and cats	23	17	—	—
Hospital patients	3	3	—	—
Urban residents	117	12	50	30
Extramural patients	168	8	—	—

* only *Enterococcus faecium*

AMGP and only in limited quantities for veterinary purposes, the prevalence of erythromycin resistance in enterococci was significantly lower, 18% and 9% respectively (17). Since 1986, Sweden has banned the use of AMGP in animal feeds. The prevalence of resistance against AMGP or related compounds in faecal samples of Swedish pigs was in 1997 significantly lower than in Dutch pigs, as shown in table III (18).

In Sweden and the USA, where avoparcin has never been used, no high level VRE (*VanA* resistance) has been found in faecal samples of food animals or in healthy humans outside hospitals (18–20). Mevius (submitted for publication) observed in Dutch veal calves from farms using avoparcin as an AMGP a significantly higher percentage VRE per gram faeces (10–100%) than in faecal samples of calves fed bacitracin as an AMGP (1–10%). The prevalence of VRE in turkey flocks fed avoparcin was 60%, in contrast to 8% in flocks not exposed to avoparcin (21). The relative odds ratio was 7.5. In Denmark, *Bager et al.* (19) found a high correlation between the usage of avoparcin on a farm and the prevalence of VRE in the intestinal flora of animals. The change of VRE isolation from the faecal samples of these animals (pigs and poultry) was three times higher in animals fed with avoparcin than from other animals. The relative odds ratio for the usage of avoparcin on the presence of VRE in the faecal flora of these animals was 2.9 (1.4–5.9) for poultry and 3.3 (0.9–12.3) for pigs. It can be concluded that the use of AMGP, like veterinary antibiotic usage, selects for resistance among susceptible microorganisms, not only in pathogens but also in bacteria belonging to the normal flora of animals like enterococci and *E. coli*. This has been shown for avoparcin, bacitracin, tylosin, virginiamycin, carbadox and olaquinox.

Table 3

Prevalence (%) of antibiotic resistant *Escherichia coli* and percentage of samples with a high degree of resistance in Swedish and Dutch faecal samples of pigs

Antibiotic	Concentration In agar (mg/l)	Sweden			The Netherlands		
		n	Prevalence	High degree	n	Prevalence	High degree
Amoxicillin	25	100	51	3	1321	85*	14**
Oxytetracycline	25	100	69	6	3121	93*	40*
Chloramphenicol	25	100	3	0	1022	63*	3
Florfenicol	25	100	0	0	1321	0	0
Nitrofurantoin	50	100	0	0	1321	3	0
Trimethoprim	8	100	46	1	1321	85*	21*
Neomycin	32	100	17	3	1321	56*	0
Gentamicin	16	100	0	0	1321	2	0
Flumequin	16	100	1	0	1321	3	0
Ciprofloxacin	4	100	0	0	1321	1	0

* Significantly higher, $P < 0.001$

** Significantly higher, $P = 0.005$

Transfer of resistant bacteria from animals to humans

Zoonotic bacteria

Most investigations on the transfer of resistant bacteria from animals to humans concern food infections caused by Gram-negative bacteria such as *Salmonella* spp., *Campylobacter* spp., and *Yersinia* spp. Transfer of resistant salmonellae from animals to humans has been described by several authors (22–25). Since the resistance of *Salmonella*-isolates from humans and animals has been monitored for many years, the emergence and dissemination of resistance in this species is very well documented. Before the introduction of antibiotics (Murray collection), isolates were fully susceptible to most antibiotics (26). Humans become infected with salmonellae from animals by direct contact with infected animals or animal faeces, but the most important source of human infection are food products of animal origin. Asymptomatic salmonella infections and carriers are common in food animals in intensive animal husbandry. Salmonellae from the intestinal tract of these animals contaminate during slaughtering carcasses, meat, and meat products and via these meat(products), eggs etc., humans can become infected.

Also humans do not always become ill after a salmonella infection. *Deleener and Haebaert* (27) showed that the frequency and variation of the different isolated *Salmonella* serotypes from asymptomatic carriers in a meat packing plant corresponded with the serotypes isolated from the supplied meat and from the produced meat products. Despite the fact that since the introduction of antibiotics in clinical medicine, resistance in human and animal isolates increased in general (28), the majority of clinical isolates are still susceptible to most antibiotics. In the Netherlands, the prevalence of tetracycline resistance in human and animal *Salmonella*-isolates increased clearly until the ban in 1969 on tetracycline use as AMGP (29), when it started to decline gradually (30–33). Also in Great Britain after this ban tetracycline resistant *S. typhimurium* isolates from calves fell from 60% in 1970 to 8% in 1977 (34). However, the spontaneous ending of epidemics by virulent tetracycline resistant *S. typhimurium* clones might have contributed to this decrease as well (35). In most EU member states, *S. enteritidis* is at this moment the most commonly isolated serotype from human infections, as a result of its extensive dissemination among poultry since 1980 (36). Because this serotype does not, in most cases, cause clinical symptoms in affected flocks, the animals are not treated with antibiotics. Therefore, the selection pressure is low and most isolates are still susceptible to most antibiotics.

Sporadically, however, epidemics of salmonella-clones with an enhanced virulence and pathogenicity for animals occur, such as *S. typhimurium* phage type 29 from 1963 till 1969, definitive type (DT) 204 in 1977, and DT 204 and DT 193 in 1980 (34). The primary reservoir of *S. typhimurium* are calves, but sheep, goats, pigs, poultry and horses can also become infected. During all these epidemics the same phage type with identical resistance profiles was isolated from animal and

human infections. Since these strains cause serious disease in affected animals, these animals were treated with antibiotics, and as a result of the selection pressure these strains tended to become (multi)resistant. Since 1994, *S. typhimurium* DT 104 has been responsible for an epidemic. This strain was from the start resistant to most of the antibiotics normally used to treat enteric infections in animals, but it has acquired in addition, resistance against trimethoprim and fluoroquinolones (28), most likely because affected groups of animals could only be treated with these antibiotics. The most important reservoir for human *Campylobacter* infections is poultry. Endtz *et al.* (13) observed that the emergence of fluoroquinolone resistant *Campylobacter jejuni* infections in humans in the Netherlands coincided with the introduction of enrofloxacin, a fluoroquinolone for poultry therapy in the spring of 1987. Enrofloxacin and ciprofloxacin, introduced in October 1988 for human therapy in the Netherlands, are fully cross-resistant. In 1989, 14% of poultry and 11% of human isolates of *C. jejuni* were resistant against ciprofloxacin. Experimentally it was shown that in flocks only colonised with ciprofloxacin susceptible *C. jejuni* after a therapy with enrofloxacin, ciprofloxacin resistant mutants emerged (37). In Great Britain, enrofloxacin was registered for veterinary use in 1993, and in that year 14% of *C. jejuni* isolates from poultry carcasses imported from the Netherlands were fluoroquinolone resistant, but nearly none of the United Kingdom isolates were (38). In 1997, however, the percentage of fluoroquinolone resistant *C. jejuni* from English broilers had approached the continental level of more than 10%. Transfer of chloramphenicol resistant *Yersinia enterocolitica* strains from animals to humans has been described by Perez-Trallero *et al.* (39).

Disturbance of colonisation resistance

Another aspect of the usage of antibiotics is the disturbance of the colonisation resistance (CR) of the intestinal flora of animals exposed to certain antibiotics (39, 40). In the case of reduced colonisation resistance, not only the minimal infection or colonisation dose of pathogenic or resistant bacteria is considerable lower, but animals excrete these bacteria in higher numbers and over a longer period of time compared to animals with an intact colonisation resistance. This enhances not only dissemination of *Salmonellae* or resistant bacteria within a group of animals, but it also increases the contamination of carcasses with these bacteria during slaughter. This effect has been clearly demonstrated for most broad-spectrum antibiotics (41) and for certain AMGP: avoparcin (42–44) and to a lesser extent, virginiamycin and tylosin (45–46). Avilamycin and bacitracin seem not to disturb the CR in the dosages used for growth promotion (47–51). Flavophospholipol has been shown to provide a certain protection against *Salmonella* infection (52).

Indicator bacteria

As a result of exposure to antibiotics, the level of resistance against antibiotics among bacteria belonging to the normal intestinal flora of humans and animals has

increased. These bacteria constitute an enormous reservoir of resistance genes for (potentially) pathogenic bacteria, but also the level of resistance in the endogenous flora is considered a good indicator for the selection pressure exerted by antibiotic use in that population (53), and for resistance problems to be expected in pathogens (54). Resistant bacteria from the intestinal flora of food animals contaminate, like zoonotic bacteria, the carcasses of slaughtered animals and reach the intestinal tract of humans via the food chain. Investigation of the prevalence of resistance of certain indicator bacteria like *E. coli* and enterococci in the intestinal tract of different populations of animals and humans makes it feasible to compare the prevalence of resistance in different populations, and to detect a possible transfer of resistant bacteria from animals to humans and vice versa. Because of the inevitable high usage of antibiotics in hospitals, selection and dissemination of resistant clones and resistance genes are high in hospitals, but emergence of new resistance due to the acquirement of new genes or gene clusters like the *VanA* gene cluster are not likely to occur in hospitals, but must once have been introduced into hospitals. Healthy individuals in the community outside hospitals are considered to be a suitable population to study the possibility of transfer of resistant bacteria or resistance genes from animals to humans and vice versa. *Corpet* (55) showed that the prevalence and degree of resistance in the faecal *E. coli* flora of humans who used only sterilised food decreased significantly. *Nijsten* (56–57) found in the faecal flora of pig farmers significantly more resistant *E. coli* than in faecal samples from pig slaughterers and (sub)urban residents. Because the personal antibiotic usage of the farmers was much higher than that of urban residents, it was difficult to draw a conclusion. However, comparison of the prevalence of ciprofloxacin resistant *E. coli* in faecal samples of turkeys and turkey farmers with pig and pig farmers strongly indicated the transfer of ciprofloxacin resistant *E. coli* strains from turkeys to turkey farmers (table IV). (18). In the Netherlands, enrofloxacin is commonly used in turkeys but not in pigs because no oral formulation for pigs was available at the time of study. Tetracyclines are used extensively in both animal species. The prevalence of ciprofloxacin resistant *E. coli* was not only significantly higher in turkey farmers and turkeys than in pig farmers and pigs, but also *E. coli* strains were isolated from farmers and turkeys which were completely identical in pulsed-field gel electrophoresis (PFGE) after

Table 4
Prevalence (%) of resistant faecal *E. coli* in different populations

Population	<i>n</i>	Ciprofloxacin	Tetracycline	Furazolidone
Turkey farmers	47	29	82	2
Turkey slaughterers	47	2	58	0
Pigs	291	2	100	17
Pig farmers	290	1	79	8
Pig slaughterers	317	0	47	4
Urban residents	117	0	31	0

*Xba*I digestion. None of the turkey farmers and suburban residents in this study had used antibiotics in the three months prior to the study. For the turkey slaughterers, the infection risk seemed much lower, despite the fact that ciprofloxacin resistant *E. coli* strains had been isolated from the turkey carcasses after slaughtering (14). In contrast, there was no difference between the prevalence of furazolidone resistant *E. coli* between the two animal populations and between the two groups of farmers, which was to be expected as furazolidone has been used extensively in both animal species. The use of furazolidone, also an antibiotic for which transferable resistance is not important, was banned for animal use in the Netherlands in 1994 and for human usage before 1980, which might explain the relatively low prevalence of resistance. These results also suggest the transfer of resistant strains from animals to humans. The extent of transfer seems to be correlated with the prevalence of resistance in the animal population, which is positively correlated with the amounts of antibiotics to which the animal population is exposed. In the same study, VRE was also isolated from a turkey farmer and from his turkeys, which were not only identical by PFGE after *Sma*I digestion, but also had a *VanA* gene with a unique mutation (58). This again strongly indicated the transfer of resistant strains from animals to humans. Moreover, in Sweden, where in 1986 all antibiotic use as AMGP has been banned, were not only none VRE detectable in the faecal flora of healthy humans and animals, it was also not detected in the stool samples of healthy volunteers after taking a course of vancomycin orally (58). In Belgium in a similar experiment, however, all volunteers, in whom no VRE was found in their stool samples before the study, became positive after taking vancomycin orally (59–60). This is in concordance with the results of *Quednau et al.* (58), who were able to isolate VRE from Danish, but not from Swedish meat(products) (61). In Swedish hospitals no *VanA*-resistance has been found in clinical enterococcal isolates (62–63). The only VRE isolated from a hospital patient contained the *VanB* gene cluster and was acquired abroad. Avoparcin does not select for the *VanB* type of resistance against glycopeptides, probably because it does not induce *vanB* resistance. Unfortunately no data on prevalence of VRE in Sweden are available from before 1986, but as until that time avoparcin was used in Sweden in a similar way as in other European countries, it is most likely that at that time VRE were common in the endogenous flora of food animals and of the general population. After the ban in Denmark the prevalence of vancomycin resistant *Enterococcus faecium* in faecal samples of broilers decreased from more than 80% in 1995 to less than 5% in 1998 (64). In contrast the prevalence in pigs ($\pm 20\%$) did not change during this time span. In Germany two years after the ban of avoparcin a decrease in the prevalence of VRE was detected in frozen and fresh poultry meats from 100% till 26% (65). In the same study a decline in the prevalence of VRE was also observed in faecal samples of healthy persons from 12% to 3%. In Italy the prevalence of VRE in poultry meats decreased within 18 months after the ban from 15% to 8% ($p = 0.01$) (66). Also in the Netherlands the prevalence of VRE in the faecal flora decreased within two years after the

ban of avoparcin significantly in broilers from 80% to 31%, in pigs from 34% to 17% and in healthy humans from 12% to 6% (67). These results point not only to avoparcin use in animals as a cause of resistance in human enterococci, but also strongly suggest that removal of the selective pressure i.e. the usage of avoparcin as AMGP, can remove VRE from a population in due time.

Transfer of resistance genes from the animal bacterial flora to pathogenic bacteria and human intestinal flora

In 1976 *Levy et al.* observed in a prospective study, that chickens fed tetracycline transfer tetracycline resistance genes between chicken *E. coli* strains, from chicken to chicken and from chicken to humans (68). A wide dissemination of a tetracycline resistance gene, *tetQ*, was observed by *Nikolich et al.* (69) and *Shoemaker et al.* (70). They found identical *tetQ* genes in host-specific intestinal flora bacteria: *Bacterioides* spp. and *Prevotella intermedius* from humans, and *Prevotella ruminicola* from bovines (49–50). The relation between the usage of an antibiotic and the dissemination of bacterial resistance from animals to humans has been described in detail by *Hummel et al.* (71). In 1982 in the former German Democratic Republic (DDR) nourseotricin, a streptotricin antibiotic was introduced as an AMGP for pigs. Streptotricin antibiotics have never been used in human or veterinary medicine and do not show cross-resistance with other antibiotics. Resistance to nourseotricin did not occur in faecal *E. coli* from pigs before the use of nourseotricin, but was within one year after its introduction, commonly found in pigs fed this antibiotic. The resistance genes were located on a transposon Tn1825, and within two years this transposon was found not only in faecal isolates from pig farmers and their family members, but also in urban residents and in *E. coli* isolated from urinary tract infections in humans. A few years later it was also found in pathogenic bacteria, not only in zoonotic bacteria like *Salmonella* spp. but also in *Shigella* spp., which only affect humans and do not have an animal reservoir. Outside the DDR nourseotricin resistance had never been found. Other examples of the dissemination of resistance genes from animals to humans are the dissemination of the *aacC4* gene (apramycin resistance) and *hphB* gene (hygromycin resistance) which are linked together, from animals to human bacteria. Despite the fact that apramycin is only used in animals (and hygromycin has never been used in humans or animals), these genes have not only been found in animal isolates or zoonotic bacteria isolated from humans, but also from *Enterobacteriaceae* in the environment, the intestinal flora of farmers, and hospital isolates (72–76).

Conclusion

In animals as in humans, the use of antibiotics causes not only an increase of resistance in pathogenic bacteria, but also in the endogenous flora of these animals. Resistant bacteria from animals (zoonotic bacteria or intestinal flora) can infect or reach the human population not only by direct contact, but also via food products

of animal origin. These resistant bacteria can either colonise humans and/or transfer their resistance genes to other bacteria belonging to the endogenous flora of man. Moreover, the greater the number of resistant bacteria in the intestinal flora, the greater the likelihood that genes encoding resistance will be transferred to (potentially) pathogenic bacteria and dissemination into the environment and from animals to food of animal origin. In this respect one might consider the resistance observed in zoonotic and nosocomial pathogens to be just the tip of the resistance iceberg. As bacteria from the human flora cannot only cause infections in immunocompromised hosts but are also considered an important reservoir of resistance genes for (potentially) pathogens, it has been proposed that a low level of carriage of resistant strains by humans should be a public health goal in much the same way as normal blood pressure and low serum cholesterol level (54). Despite the fact that it is not clear yet to what extent the use of antibiotics in animals contributes to the resistance problems in human medicine, it cannot be disputed that it is a certain factor. Since we are now encountering in human medicine some microorganisms that are so multiresistant that it is difficult, and may soon be impossible, to fight these with the clinically available antibiotics, every source of resistance must be controlled as much as feasible. Therefore, a low level of resistance in the intestinal flora of food animals should be thought of as a safety and distinguishing benchmark for food animals (15, 77). Moreover, this will not only protect public health, but also safeguard the future efficacy of antibiotics in veterinary medicine. This goal can only be achieved by reducing the amounts of antibiotics used in animals. The requirement for antibiotics in veterinary therapy and bacterial infection prevention in animals should be minimised by improving methods of animal husbandry, disease eradication, optimal usage of existing vaccines, and the development of new vaccines. If antibiotics have to be used, the usage of small spectrum molecules should be preferred and it should be done according to a sensible veterinary antibiotic policy (78). Discontinuing the practice of routinely adding AMGP to animal feeds would reduce the amounts of antibiotics used for animals in the EU by a minimal 30% and in some countries even by 50%. In this case the public health risks should be weighed against the economical profits and/or alternatives to AMGP, such as pre- and probiotics, which should be developed. The Swedish have shown that modern and profitable animal husbandry without AMGP is feasible (79).

Summary

An inevitable side effect of the use of antibiotics is the emergence and dissemination of resistant bacteria not only in pathogenic bacteria but also in the endogenous flora of man and animals. Resistant commensal bacteria of food animals might contaminate, like zoonotic bacteria, meat (products) and so reach the intestinal tract of humans. Resistance genes against antibiotics that are or have only been used in animals were soon after their introduction not only found in animal bacteria, but also in the commensal flora of humans, in zoonotic pathogens like *Salmonellae*, but

also in strictly human pathogens, like *Shigellae*. This makes it clear that not only clonal spread of resistant strains occurs, but also transfer of resistance genes between human and animal bacteria. Moreover, since the EU ban of avoparcin, in several European countries a significant decrease in the prevalence of vancomycin resistant enterococci in meat(products), in faecal samples of food animals and of healthy humans has been observed, which underlines the role of antimicrobial usage in food animals in the selection of bacterial resistance and the transport of these resistances via the food chain to humans.

To safeguard public health the therapeutic use of antibiotics in animals should be reduced and the use of antibiotics as growth promoters stopped.

Zusammenfassung

Ein unvermeidbarer Nachteil in der Anwendung von Antibiotika ist das Entstehen und die Ausbreitung von resistenten Bakterien, nicht nur bei pathogenen Bakterien, sondern auch in der endogenen Flora bei Mensch und Tier. Resistente kommensale Bakterien von Schlachttieren können, wie auch die tiereigenen Bakterien, Fleischprodukte und somit dann den Intestinaltrakt des Menschen kontaminieren. Resistenzgene gegen Antibiotika, die lediglich in Tieren angewandt wurden, wurden bald nach ihrer Einführung nicht nur bei Tieren gefunden, sondern in der kommensalen Flora beim Menschen, in tierischen Pathogenen wie *Salmonella*, aber auch in rein menschlichen Pathogenen, wie *Shigella*-Stämmen. Dies zeigt, dass nicht allein eine klonale Verbreitung von resistenten Stämmen auftritt, sondern auch ein Transfer von resistenten Genen zwischen menschlichen und tierischen Bakterien stattfindet. Mehr noch, seit dem EU-Verbot von Avoparcin ist in mehreren europäischen Ländern eine bedeutende Verringerung der sonst vorherrschenden vancomycinresistenten Enterokokken in Fleischprodukten, in Fäkalproben von Tieren für die Lebensmittelindustrie und von gesunden Menschen beobachtet worden. Das unterstreicht doch die Rolle der antimikrobiellen Anwendung bei Tieren in ihrer Selektion von bakterieller Resistenz und dem Transport dieser Resistenzen via Lebensmittelkette zu den Menschen.

Um die Volksgesundheit zu gewährleisten, ist die therapeutische Anwendung von Antibiotika bei Tieren zu reduzieren und der Gebrauch von Antibiotika als Wachstumsförderer zu stoppen.

Résumé

Une conséquence inévitable de l'utilisation des antibiotiques dans l'alimentation animale a été l'émergence et la dissémination de souches des bactéries résistantes. Il peut s'agir de bactéries pathogènes mais également de souches provenant de la flore endogène de l'homme et de l'animal. Les bactéries commensales des animaux à viande auraient la capacité, à l'instar des bactéries zoonotiques, de contaminer les produits carnés et d'atteindre ainsi le tractus gastro-intestinal humain. On a pu constater, chez des bactéries animales mais aussi chez des bactéries commensales de

l'humain, chez des pathogènes comme *Salmonellae* et même chez des pathogènes strictement humains tels que *Shigellae*, des gènes de résistance à des antibiotiques qui n'ont été utilisés que chez l'animal. Cela apporte clairement la preuve d'un transfert de gènes de résistance entre les bactéries humains et animales. De surcroît, depuis l'interdiction de l'avoparcine en Europe, on a pu constater une diminution significative de la prévalence d'entérocoques résistants à la vancomycine dans les produits carnés aussi bien que dans les selles des animaux à viande et également dans les selles des humains sains. Ceci met en évidence le rôle que les antibiotiques utilisés dans l'alimentation animale jouent dans la sélection de résistances bactériennes et dans le transport de ces résistances jusqu'à l'humain par le biais de la chaîne alimentaire.

Dans l'intérêt de la santé publique, il serait judicieux de réduire l'utilisation thérapeutique d'antibiotiques chez l'animal et de stopper leur utilisation comme facteur de croissance.

Key words

Resistance, Antibiotic, Animal, Feed, Human, Food

References

- 1 Swann, M.: Joint Committee on the use of antibiotics in animal husbandry and veterinary medicine. London: Her Majesty's Stationary Office, London 1969.
- 2 Devriese, L.A., Daube, G., Homme, J. and Haesebrouk, F.: In vitro susceptibility of *Clostridium perfringens* isolated from farm animals to growth enhancing antibiotics. J. Appl. Bacteriol. **75**, 55–57 (1993).
- 3 Dutta, G.N. and Devriese, L.A.: Susceptibility of faecal streptococci of poultry origin to nine growth-promoting agents. Appl. Environ. Microbiol., **44**, 832–837 (1982).
- 4 Antimicrobial feed additives. Report from the Commission on antimicrobial feed additives. The Ministry of Agriculture of Sweden. Stockholm: Government Official Reports, SOU, (1997).
- 5 Prescott, J.F. and Baggot, J.D.: Antimicrobial therapy in veterinary medicine. Iowa State University Press, Ames 1993.
- 6 Linton, A.H., Hinton, M.H. and Al Chalaby, Z.A.M.: Monitoring for antibiotic resistance in enterococci consequent upon feeding growth promoters active against Gram-positive bacteria. J. Vet. Pharmacol. Ther. **8**, 62–70 (1985).
- 7 Linton, A.H., Hedges, A.J. and Bennet, P.M.: Monitoring for the development of resistance during the use of olaquinox as a feed additive on commercial pig farms. J. Appl. Bacteriol. **64**, 311–327 (1988).
- 8 Ohmae, K., Yonezawa, S. and Terakado, N.: Epizootiological studies on R-plasmid with carbadox resistance. Jap. J. Vet. Sci. **45**, 165–170 (1983).
- 9 Ohmae, K., Yonezawa, S. and Terakado, N.: R-plasmid with carbadox resistance from *Escherichia coli* of porcine origin. Antimicrob. Agents Chemother. **19**, 86–90 (1981).
- 10 Mills, K.W. and Kelly, B.L.: Antibiotic susceptibilities of swine *Salmonella* isolates from 1979 to 1983. Am. J. Vet. Res. **47**, 2349–2350 (1986).
- 11 Bates, J., Jordens, J.Z. and Griffiths, D.T.: Farm animals as a putative reservoir for vancomycin resistant enterococcal infection in man. J. Antimicrob. Chemother. **34**, 507–516 (1994).

- 12 Edlund, C., Barkholt, L., Olsson-Liljequist, B. and Nord, C.E.: Impact of peroral treatment with vancomycin on the human intestinal microflora. Proceedings of the 37th ICAAC Conference Toronto. ASM Washington, DC 1997.
- 13 Endtz, H.P., Ruijs, G.J., van Klingeren, B., Jansen, W.H., van der Reyden, T. and Mouton, R.P.: Quinolone resistance in *Campylobacter* isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine. J. Antimicrob. Chemother. **37**, 1197–1199 (1991).
- 14 Van den Bogaard, A.E., London, N., Driessen, C. and Stobberingh, E.: Prevalence of resistant faecal bacteria in turkeys, turkey farmers, and turkey slaughterers. Proceedings of the 36th ICAAC Conference, New Orleans. ASM Washington, DC 1996.
- 15 Van den Bogaard, A.E., Mertens, P., London, N., Driessen, C. and Stobberingh, E.: High prevalence of colonisation with vancomycin and pristinamycin resistant enterococci in healthy humans and pigs in the Netherlands. J. Antimicrob. Chemother. **40**, 453–454 (1997).
- 16 DANMAP 1995. Consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. No. 1. Copenhagen, Statens Vekinase Institue 1997.
- 17 Tast, E.: Tylosin and spiramycin as feed additives., influence on the efficacy of therapeutic macrolides. Report of the Ministry of Agriculture and Forestry of Finland. Julkaisuja, Helsinki 1997.
- 18 Van den Bogaard, A.E., London, N. and Stobberingh, E.: Antimicrobial resistance in pig faecal samples from the Netherlands and Sweden. J. Antimicrob. Chemother. **45**, 663–671 (2000).
- 19 Bager, F., Madson, M., Christensen, J. and Aarestrup, F.: Avoparcin used as growth promoter is associated with the occurrence of vancomycin resistant *E. faecium* in Danish poultry and pig farms. Prev. Vet. Med. **31**, 95–112 (1997).
- 20 Coque, T.M., Tomayko, J.F., Rick, S.C., Okhuysen, P.C. and Murray, B.E.: Vancomycin resistant enterococci in nosocomial and community, and animal sources in the USA. Antimicrob. Agents Chemother. **40**, 2605–2609 (1996).
- 21 Van den Bogaard, A.E., London, N., Driessen, C. and Stobberingh, E.: Fluoroquinolone usage in animals and resistance in human faecal *E. coli*. Proceedings 37th ICAAC Conference Toronto 1997. ASM Washington, DC 1997.
- 22 Bezanson, G.S., Khakhria, R. and Bollegraaf, E.: Nosocomial outbreak caused by antibiotic resistant strain of *Salmonella typhimurium* acquired from dairy cattle. Can. Med. Assoc. J. **128**, 426–427 (1983).
- 23 Holmberg, S.D., Osterholm, M.T., Senger, K.A. and Cohen, L.: Drug resistant salmonella from animals fed antimicrobials. N. Engl. J. Med. **311**, 617–622 (1984).
- 24 McDonald, L.C., Kuehnert, M.J., Tenover, F.C. and Jarvis, W.R.: Vancomycin resistant enterococci outside the healthcare setting: prevalence, sources, and public health implications. Emerg. Infect. Dis. **3**, 311–317 (1997).
- 25 Spika, J.S., Waterman, S.H. and Hoo, G.W.: Chloramphenicol resistant *Salmonella newport* traced through hamburger to dairy farms. A major persisting source of human salmonellosis in California. N. Engl. J. Med. **316**, 565–570 (1987).
- 26 Datta, N. and Hughes, V.M.: Plasmids of the same *Inc* groups in *Enterobacteria* before and after the medical usage of antibiotics. Nature **306**, 616–617 (1983).
- 27 Deleener, J. and Haebaert, K.: Enquête sur la role joué dans propagation de *Salmonella* et *Shigella* par les porteurs de germes dans l'industrie de la viande. Med. Mal. Infect. **10**, 394–398 (1980).
- 28 Wray, C.: Medical impact of antimicrobial use in food animal production: scenarios and risk assessment *Salmonella* and *E. coli* in England and Wales. Proceedings of the WHO meeting on the usage of quinolones in animals. WHO, Geneva 1997.

- 29 *Manten, A., Guinee, P.A., Kampelmacher, E.H. and Voogd, C.E.*: An 11 years study of drug resistance in *Salmonella* in the Netherlands. *Bull. World Health Organ.* **5**, 85–93 (1971).
- 30 *Leeuwen, W.J., van Voogd, C.E., Guinee, P.A.M., Manten, A. and van Leeuwen, W.J.*: Incidence of resistance to ampicillin, chloramphenicol, kanamycin, tetracycline and trimethoprim of *Salmonella* strains isolated in the Netherlands during 1975–1980. *Antonie van Leeuwenhoek* **48**, 85–96 (1982).
- 31 *Voogd, C.E., Guinee, P.A., Manten, A. and Kampelmacher, E.H.*: Incidence of resistance to tetracycline, chloramphenicol and ampicillin among *Salmonella* species isolated in the Netherlands in 1965 and 1966. *Antonie van Leeuwenhoek* **34**, 357–364 (1968).
- 32 *Voogd, C.E., Guinee, P.A., Manten, A. and Valkenburg, J.J.*: Incidence of resistance to tetracycline, chloramphenicol and ampicillin among *Salmonella* species isolated in the Netherlands in 1967 and 1968. *Antonie van Leeuwenhoek* **36**, 297–304 (1970).
- 33 *Voogd, C.E., van Leeuwen, W.J., Guinee, P.A., Manten, A. and Valkenburg, J.J.*: Incidence of resistance to ampicillin, chloramphenicol, kanamycin and tetracycline among *Salmonella* species isolated in the Netherlands in 1972, 1973 and 1974. *Antonie van Leeuwenhoek* **43**, 269–281 (1977).
- 34 *Cherubin, C.E.*: Epidemiological assessments of antibiotic resistance in *Salmonella*. In: *Steel, J.H. and Beran, G.W.*, (eds.), *CRC handbook series in zoonoses*, p. 173–200. CRC Press Inc, Boca Raton 1984.
- 35 National Academy of Sciences. Committee to study the human health aspects of subtherapeutic antibiotic use in animal feeds. National Press Washington DC 1980.
- 36 *Mishu, B., Griffin, P.M., Tauxe, R.V., Cameron, D.N., Hutcheson, R.H. and Schaffner W.*: *Salmonella enteritidis* gastroenteritis transmitted by intact chicken eggs. *Ann. Intern Med.* **115**, 190–194 (1991).
- 37 *Jacobs-Reitsma, W.F., Kan, C.A. and Bolder, N.M.*: The induction of quinolone resistance in *Campylobacter* bacteria in broilers by quinolone treatment. *Lett. Appl. Microbiol.* **19**, 228–231 (1994).
- 38 *Gaunt, P.N. and Piddock, L.J.V.*: Ciprofloxacin resistant *Campylobacter* in humans: an epidemiological and laboratory study. *J. Antimicrob. Chemother.* **37**, 747–757 (1996).
- 39 *Perez-Trallero, E., Zigortraga, C., Cilla, G., Idigoras, P., Lopez-Lopategui, C. and Solaun, L.*: Animal origin of the antibiotic resistance of human pathogenic *Yersinia enterocolitica*. *Scand. J. Infect. Dis.* **20**, 572–573 (1988).
- 40 *Van der Waaij, D.*: Colonisation resistance of the digestive tract: clinical consequences and implications. *J. Antimicrob. Chemother.* **10**, 263–270 (1982).
- 41 *Vollaard, E.J., Clasener, H.A.L., van Saene, H.K.F. and Muller, N.F.*: Effect on colonisation resistance: an important criterion in selecting antibiotics. *Ann. Pharmacother.* **24**, 60–66 (1990).
- 42 *Barrow, P.A.*: Further observations on the effect of feeding diets containing avoparcin on the excretion of *Salmonella* by experimentally infected chickens. *Epidemiol. Infect.* **102**, 239–252 (1989).
- 43 *Barrow, P.A., Williams-Smith, H., Tucker, J.F. and Smith, H.W.*: The effect of feeding diets containing avoparcin on the excretions of salmonellas by chickens experimentally infected with natural sources of *Salmonella*. *J. Hygiene* **93**, 439–444 (1984).
- 44 *Gustafson, R.H., Beck, J.R. and Kobland, J.D.*: The influence of avoparcin on the establishment of *Salmonella* in chickens. *Zentralblatt Vet. Med. B* **29**, 119–128 (1982).
- 45 *Abou-Youssef, M.H., DiCuollo, C.J., Miller, C.R. and Scott, G.C.*: 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 (1979).
- 46 *George, B.A., Fagerberg, D.J., Quarles, C.L., Fenton, J.M. and McKinley, G.A.*: Effect of bambermycins on quantity, prevalence, duration, and antimicrobial resistance of *Salmonella typhimurium* in experimentally infected broiler chickens. *Am. J. Vet. Res.* **43**, 299–303 (1982).

- 47 Humbert, F., Lalande, F., L'Hospitalier, R., Salvat, G. and Bennegean, G.: Effect of four antibiotic additives on the *Salmonella* contamination of chicks protected by an adult faecal flora. *Avian Path.* **20**, 577–584 (1991).
- 48 Matthes, S., Leuchtenberger, W.G. and Loliger, H.C.: Influence of antibiotic feed additives on the intestinal flora and persistence of *Salmonella* in chicks. *Deut. Tierärztl. Wschr.* **89**, 19–22 (1982).
- 49 Nurmi, E. and Rantala, M.: The influence of zinc bacitracin on the colonisation of *Salmonella infantis* in the intestine of broiler chickens. *Res. Vet. Sci.* **17**, 24–27 (1974).
- 50 Smith, H.W. and Tucker, J.F.: The effect of antimicrobial feed additives on the colonisation of the alimentary tract of chickens by *Salmonella typhimurium*. *J. Hygiene* **80**, 217–231 (1978).
- 51 Smith, H.W. and Tucker, J.F.: The effect of feeding diets containing permitted antibiotics on the faecal excretion of *Salmonella typhimurium* by experimentally infected chickens. *J. Hygiene* **75**, 293–301 (1975).
- 52 Ford, A.M., Fagerberg, D.J., Quarles, C.L., George, B.A. and McKinley, G.A.: Influence of salinomycin on incidence, shedding, and antimicrobial resistance of *Salmonella typhimurium* in experimentally infected broiler chicks. *Poult. Sci.* **60**, 2441–2453 (1981).
- 53 Murray, B.E.: Problems and dilemmas of antimicrobial resistance. *Pharmacotherapy* **12**, 86–93 (1992).
- 54 Lester, S.C., del Pilar Pla, M., Wang, F., Perez Schael, I., Jiang, H. and O'Brien, T.: The carriage of *Escherichia coli* resistant to antimicrobial agents by healthy children in Boston, in Caracas, Venezuela, and in Qin Pu, China. *N. Engl. J. Med.* **323**, 285–289 (1990).
- 55 Corpet, D.: Antibiotic resistance from food. *N. Engl. J. Med.* **318**, 1206–1207 (1988).
- 56 Nijsten, R., London, N., van den Bogaard, A. and Stobberingh, E.: Antibiotic resistance among *Escherichia coli* isolated from faecal samples of pig farmers and pigs. *J. Antimicrob. Chemother.* **37**, 1131–1140 (1996).
- 57 Nijsten, R., London, N., van den Bogaard, A. and Stobberingh, E.: Resistance in faecal *Escherichia coli* isolated from pig farmers and abattoir workers. *Epidemiol. Infect.* **113**, 45–52 (1994).
- 58 Van den Bogaard, A.E., Jensen, L.B. and Stobberingh, E.E.: Vancomycin resistant enterococci in turkeys and farmers. *N. Engl. J. Med.* **337**, 1558–1559 (1997).
- 59 Quednau, M., Abrne, S., Petersson, A.C. and Molin, G.: Antibiotic resistant strains of enterococcus isolated from Swedish retailed chicken and pork. *J. Appl. Microbiol.* **84**, 1163–1170 (1998).
- 60 Van der Auwera, P., Pensart, N., Korten, V., Murray, B.E. and Leclerque, R.: Influence of oral glycopeptides on the faecal flora of human volunteers: selection of highly glycopeptide resistant enterococci. *J. Infect. Dis.* **173**, 1129–1236 (1996).
- 61 Vollaard, E.J. and Clasener, H.A.L.: Colonisation resistance. *Antimicrob. Agents Chemother.* **38**, 409–414 (1994).
- 62 Torell, E., Fredlund, H., Tornquist, E., Myhre, E.B., Sjoberg, L. and Sundsfjord, A.: Intrahospital spread of vancomycin-resistant *Enterococcus faecium* in Sweden. *Scand. J. Infect. Dis.* **29**, 259–263 (1997).
- 63 Torell, E., Cars, O., Olsson Liljequist, B., Hoffman, B.M., Lindback, J. and Burman, L.G.: Near absence of vancomycin-resistant enterococci but high carriage rates of quinolone-resistant ampicillin-resistant enterococci among hospitalised patients and non-hospitalised individuals in Sweden. *J. Clinical Microbiol.* **37**, 3509–3513 (1999).
- 64 Bager, F., Aarestrup, F.M., Madsen, M. and Wegener, H.C.: Glycopeptide resistance in *Enterococcus faecium* from broilers and pigs following discontinued use of avoparcin. *Microbial Drug Resistance Mechanisms Epidemiology and Disease* **5**, 53–56 (1999).
- 65 Klare, I., Badstubner, D., Konstabel, C., Bohme, G., Claus, H. and Witte, W.: Decreased incidence of VanA-type vancomycin-resistant enterococci isolated from poultry meat and from faecal samples of humans in the community after discontinuation of avoparcin usage in animal husbandry. *Microbial Drug Resistance Mechanisms Epidemiology and Disease* **5**, 45–52 (1999).

- 66 Pantosti, A., Del Grosso, M., Tagliabue, S., Macri, A. and Caprioli, A.: Decrease of vancomycin resistant enterococci in poultry meat after avoparcin ban. *Lancet* **354**, 741–742 (1999).
- 67 Van den Bogaard, A.E., Bruinsma, N. and Stobberingh, E.E.: The effect of banning avoparcin on VRE carriage in the Netherlands. *J. Antimicrob. Chemother.* **46**, 146–148 (2000).
- 68 Levy, S.B., FitzGerald, G.B. and Maccone, A.B.: Spread of antibiotic resistance plasmids from chicken to chicken and from chicken to man. *Nature* **260**, 40–42 (1976).
- 69 Nikolich, M.P., Hong, G., Shoemaker, N.B. and Salyers, A.A.: Evidence for natural horizontal transfer of *tetQ* between bacteria that normally colonise humans and bacteria that normally colonise livestock. *Appl. Environ. Microbiol.* **60**, 3255–3260 (1994).
- 70 Shoemaker, N.B., Wang, G. and Salyers, A.A.: Evidence for natural transfer of a tetracycline resistance gene between bacteria from the human colon and bacteria from the bovine rumen. *Appl. Environ. Microbiol.* **58**, 1313–1320 (1992).
- 71 Hummel, R., Tschäpe, H. and Witte, W.: Spread of plasmid-mediated nourseothricin resistance due to antibiotic use in animal husbandry. *J. Basic Microbiol.* **8**, 461–466 (1986).
- 72 Chaslus-Dancla, E., Glupczynski, Y., Gerbaud, G., Lagorce, M., Lafont, J.P. and Courvalin, P.: Detection of apramycin resistant *Enterobacteriaceae* in hospital isolates. *FEMS Microbiol. Lett.* **61**, 261–266 (1989).
- 73 Chaslus-Dancla, E., Martel, J.L., Carlier, C., Lafont, J.P. and Courvalin, P.: Emergence of aminoglycosides 3-N-acetyltransferase IV in *Escherichia coli* and *Salmonella typhimurium* isolated from animals. *Antimicrob. Agents Chemother.* **29**, 239–243 (1986).
- 74 Chaslus-Dancla, E., Pohl, P., Meurisse, M., Martin, M. and Lafont, J.P.: High genetic homology between plasmids of human and animal origins conferring resistance to the aminoglycosides gentamicin and apramycin. *Antimicrob. Agents Chemother.* **35**, 590–593 (1991).
- 75 Hunter, J.E.B., Bennett, M., Hart, C.A., Shelley, J.C. and Walton, J.R.: Apramycin resistant *Escherichia coli* isolated from pigs and a stockman. *Epidemiol. Infect.* **112**, 473–480 (1994).
- 76 Tresfall, E.J., Rowe, B., Ferguson, J.L. and Ward, L.R.: Characterisation of plasmids conferring resistance to gentamicin and apramycin in strains of *Salmonella typhimurium* phage type 204c isolated in Britain. *J. Hyg. Camb.* **97**, 419–426 (1986).
- 77 Van den Bogaard, A.E. and Stobberingh, E.E.: Time to ban all antibiotics as animal growth promoting agents? Reply and authors' reply. *Lancet* **348**, 1454–1456 (1996).
- 78 Wray, C., Hedges, R.W., Shannon, K.P. and Bradley, D.E.: Apramycin and gentamicin resistance in *Escherichia coli* and *Salmonella* isolated from farm animals. *J. Hyg. Camb.* **97**, 445–456 (1986).
- 79 Van den Bogaard, A.E., Jensen, L.B. and Stobberingh, E.E.: A veterinary antibiotic policy, a personal view on the perspectives in the Netherlands. *Vet. Microbiol.* **35**, 303–312 (1993).

Corresponding author: Dr. Anthony van den Bogaard, University Hospital Maastricht, Department Medical Microbiology, P.O. Box 616, NL-6200 MD Maastricht
E-mail: A.vandenBogaard@CPV.UNIMAAS.NL