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Epidemiology of resistance to antibiotics Links between animals and humans

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Abstract

An inevitable side effect of the use of antibiotics is the emergence and dissemination of resistant bacteria. Most retrospective and prospective studies show that after the introduction of an antibiotic not only the level of resistance of pathogenic bacteria, but also of commensal bacteria increases. Commensal bacteria constitute a reservior of resistance genes for (potentially) pathogenic bacteria. Their level of resistance is considered to be a good indicator for selection pressure by antibiotic use and for resistance problems to be expected in pathogens. Resistant commensal bacteria of food animals might contaminate, like zoonotic bacteria, meat (products) and so reach the intestinal tract of humans. Monitoring the prevalence of resistance in indicator bacteria such as faecal *Escherichia coli* and enterococci in different populations, animals, patients and healthy humans, makes it feasible to compare the prevalence of resistance and to detect transfer of resistant bacteria or resistance genes from animals to humans and vice versa. Only in countries that use or used avoparcin (a glycopeptide antibiotic, like vancomycin) as antimicrobial growth promoter (AMGP), is vancomycin resistance common in intestinal enterococci, not only in exposed animals, but also in the human population outside hospitals. Resistance genes against antibiotics, that are or have only been used in animals, i.e. nourseothricin, apramycin etc. were found soon after their introduction, not only 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, a significant decrease has been observed in several European countries in the prevalence of vancomycin resistant enterococci in meat (products), in faecal samples of food animals and healthy humans, 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 selection and dissemination of resistant bacteria from animals should be controlled. This can only be achieved by reducing the amounts of antibiotics used in animals. Discontinuing the practice of routinely adding AMGP to animal feeds would reduce the amounts of antibiotics used for animals in the EU by a minimum of 30% and in some member states even by 50%.

Keywords: Antibiotic resistance; Animals; Humans; Indicator bacteria; Antimicrobial growth promoters

1. Introduction

World wide there is growing concern about the increased prevalence of antibiotic resistance. It is now generally accepted that the main risk factor for this increase in resistance in pathogenic bacteria is the increased use of antibiotics. This has inevitable lead to the emergence and dissemination of resistant bacteria and resistance genes. This situation applies to antibiotic usage both in animals and in humans. In both populations antibiotics are used for therapy and prophylaxis of infectious diseases.

Approximately 50% of all antibacterial agents used annually in the EU are given to animals [1]. These antibiotics are not only used in veterinary indication for therapy and prevention of bacterial infections, but may also be added continuously to animal feeds to promote growth, increase feed efficacy and decrease waste production. The antibiotics used for this purpose are commonly called feed savers, antimicrobial growth promoters or performance enhancers (APE). In Europe,

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approximately 30% of all antibiotics used in animals are used as APE, but large differences between the EU-member states exist [1]. Because the recommendations of the Swann report [2] in 1969 have been followed by most EU-member states, molecules that are used for therapy in humans and/or animals may not be used as APE. However, many of the APE that are used today in the EU are analogues of and show cross resistance with therapeutic antibiotics. APE are mainly active against Gram-positive bacteria [3,4] (Table 1) [5], with the exception of carbadox and olaquindox, which are mainly active against Gram-negatives [6]. Approximately 90% of all antibiotics used for veterinary purposes are given orally to food animals like poultry, pigs and calves, mostly mixed in the feed, but sometimes poured over the feed or dissolved in the drinking water or milk. In the Netherlands, APE are included in nearly all feeds for pigs, broilers and veal calves and the amount of antibiotics used as APE is of the same size of order as that for veterinary purposes, 250 versus 300 tonnes of active drug [7]. In other countries such as the UK the veterinary use is more than three times as high as the use for growth promotion.

2. Resistance

Many retrospective and prospective studies have been performed to study the emergence and selection of resistance in bacteria from animals by antibiotic usage. Despite large differences in methodology, most results show that after the introduction of an antibiotic in veterinary practise, the resistance in pathogenic bacteria and/or the faecal flora increases, as in human medicine. Some bacteria, most enterobacteriaceae, staphylococci and *Pasteurella* spp. become more readily resistant to certain antibiotics than others like *Clostridium* spp. and streptococci which are still fully susceptible to penicillin G.

The literature on resistance against APE is very limited as most of these molecules are not used for therapy and therefore, susceptibility testing is not performed regularly. Linton [8] found a significant increase in the prevalence of resistance against tylosin and bacitracin in faecal enterococci of pigs and poultry fed these molecules. In this study, virginiamycin usage did not result in an increase in resistance. The prevalence of resistance in faecal *Escherichia coli* from pigs to olaquindox increased in 3 years from 0.004 to 6% after the introduction of olaquindox to farms as APE in 1982 whereas in farms not using olaquindox the prevalence of resistance increased as well, but to a significantly lesser degree suggesting dissemination of resistant clones [9]. Ohmae [10,11] noticed an increase of resistance against carbadox in faecal *E. coli* isolates of pigs after its introduction as APE. All resistant isolates from six farms that fed carbadox continuously to pigs either as APE or for 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 [12] also reported an increase in resistance in *E. coli* isolates from 37 to 61% after the introduction of carbadox. Carbadox, however, was not only used as an APE, but also for prevention of swine dysentery and therapy for salmonellosis.

Interest in the selection of resistance by APE increased after the emergence of vancomycin resistant enterococci (VRE) in human infections. It was soon recognised that avoparcin was until recently commonly used as APE in most EU-member states, selects for VRE in the intestinal flora of animals [13]. In countries where avoparcin was used as APE, VRE was not only found in food animals fed with avoparcin, but also in the faecal flora of healthy humans and pet animals [14–17] (Table 2). Also resistance against MLS-antibiotics like erythromycin and quinupristin–dalfopristin

Table 1
Normal susceptibility ranges of clostridia and enterococci for antimicrobial performance enhancers and permitted levels in animals feeds (modified from [3,4])

Antibacterial substances	Class (and a therapeutic equivalent)	Range of minimum inhibitory concentrations (mg/l)	Dosage used for performance enhancement (mg/kg feed)	
			Clostridium spp.	*Enterococcus* spp.
Avilamycin	Enverninomycins (everninomycin)	0.25–0.5	Not done	2.5–40
Avoparcin	Glycopeptides (vancomycin)	0.5–2	1–2	5.40
Bacitracin	Polypeptides (bacitracin)	1–4[2]	<0.5–16	5–100
Flavomycin	Bambermycins	<1–8	0.25–4	1–25
Monesin	Polyethers	0.5–4	1–2	10–40
Tylosin	Macrolides (erythromycin)	<1	1–4	4–40
Spiramycin	Macrolides (spiramycin)	0.25–8	0.5–4	5–80
Virginiamycin	Pristinamycins (quinupistin–dalfopristin)	0.25–1	0.25–8	5–80

Table 2
Prevalence of vancomycin, erythromycin and pristinamycin resistant enterococci in the faecal flora of healthy animals and humans in the Netherlands[a]

Population	*N*	Prevalence of resistance		
		Vancomycin *Van*A	Erythromycin	Quinupristin–dalfopristin[b]
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
Outpatients	168	8	–	–

[a] D. Mevius, submitted for publication.
[b] Only *E. faecium* included.

Table 3
Prevalence (%) of antibiotic resistant *E. coli* and percentage of samples with a high level of resistance (>50% of the total number of *E. coli* resistant) in Swedish and Dutch faecal samples of pigs

Antibiotic	Concentration in agar (mg/l)	Sweden			The Netherlands		
		N	Prevalence	High level resistance	*N*	Prevalence	High level resistance
Amoxycillin	25	100	51	3	1321	85*	14**
Oxytetracyline	25	100	69	6	1321	93*	40*
Chloramphenicol	25	100	3	0	1022	63*	3
Florfenicol	25	100	0	0	1321	0	0
Nitrofurantion	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 ($P=0.005$).

(Synercid®) is quite common in enterococci from animals fed with related antibiotics as APE like tylosin (a macrolide) or virginiamycin (a combination of two pristinamycins like quinupristin–dalfopristin) [15]. Similar figures have been found in other European countries like Denmark [18], 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, where tylosin is not used as APE and only in a limited fashion for veterinary purposes, the prevalence of erythromycin resistance in enterococci is significantly lower, 18 and 9%, respectively [19].

Sweden has banned the usage of APE in animal feeds since 1986. The prevalence of resistance against APE or related compounds in faecal samples of Swedish pigs in 1997 was significantly lower than in Dutch pigs, as shown in Table 3 [20]. In Sweden and the USA, where avoparcin has never been used, no high level VRE (*Van*A resistance) has been found in faecal samples of food animals or healthy humans outside hospitals [20–22].

Mevius (submitted for publication) observed a significantly higher percentage VRE per gram faeces (10–100%) in veal calves from farms using avoparcin as APE than in faecal samples of calves fed with bacitracin as APE (1–10%). The prevalence of VRE in turkey flocks fed with avoparcin was 60% in contrast to 8% in flocks not exposed to avoparcin [16]. The relative odds ratio was 7.5. In Denmark, Bager et al. [22] found a high correlation between the usage of avoparcin on a farm and the prevalence of VRE in the intestinal flora of animals. The chance of isolation VRE from faecal samples of 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. Moreover, after the ban of

avoparcin in Denmark the occurrence of vancomycin resistant *E. faecium* in faecal samples of broilers declined significantly from more than 80% in 1995 to less than 5% in 1998. However, the prevalence in pig faecal samples remained constant at approximately 20% [23].

It can also be concluded that the use of APE-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 such as enterococci and *E. coli*. This has been shown for avoparcin, bacitracin, tylosin, virginiamycin, carbadox and olaquindox. In poultry, withdrawal of avoparcin resulted in a decrease of glycopeptide resistance.

3. Transfer of resistant bacteria from animals to human

3.1. Zoonotic bacteria

Most investigations on the transfer of resistant bacteria from animals to human concern Gram-negative food infections caused by bacteria such as *Salmonella* spp., *Campylobacter* spp. and *Yersinia* spp. Transfer of resistant salmonellae from animals to human has been described by several authors [24–27]. Because 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 [28]. Humans become infected with salmonellae from animals by direct contact with infected animals or animal faeces but the most important source of human infections are food products of animal origin. Asymptomatic *Salmonella* infections and carriers are common in food animals in intensive animal husbandry. The salmonellae in the intestinal tract of these animals contaminate meat and meat products during slaughtering and humans can become infected via meat (products), eggs etc. Humans do not always become ill after a *Salmonella* infection. Deleener and Haebaert [29] 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 manufactured meat products. Despite the fact that since the introduction of antibiotics in clinical medicine resistance in human and animal isolates increased in general [30], the majority of clinical isolates are still susceptible to most antibiotics. In the Netherlands, the prevalence of tetracycline resistance in human and animal salmonellae isolates increased until the ban on tetracycline as APE [31], when it started to decline gradually [32–35]. Also in Great Britain tetracycline resistant *S. typhimurium* isolates from calves fell down from 60% in 1970 to 8% in 1977 after the ban on tetracycline as APE [36]. However, the spontaneous ending of epidemics by virulent tetracycline resistant *S. typhimurium* clones might have contributed to this decrease as well [37]. In most EU-member states *S. enteritidis* is the most commonly isolated serotype from human infections, as a result of its extensive dissemination among poultry since 1980. Because this serotype does not cause clinical symptoms in affected flocks in most cases, 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 occurred, 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 [36]. The primary reservoir of *S. typhimurium* are calves, but also sheep, goats, pigs, poultry and horses can become infected. During all these epidemics the same phage type with identical resistance profiles was isolated from animal and human infections. Because these strains cause serious disease in affected animals, these animals are treated with antibiotics and as a result of the selection pressure these strains tend to become (multi)resistant. Since 1994 *S. typhimurium* DT 104 has been causing an epidemic. This strain was resistant to most of the antibiotics normally used to treat enteric infections in animals from the start, but it has acquired in addition resistance against trimethoprim and fluoroquinolones [30], most likely because affected groups of animals could only be treated with these antibiotics. Recently an outbreak of 25 human cases with fluoroquinolone resistant *S. typhimurium* DT 104 has been described in Denmark. The molecular epidemiology and patient data indicated clearly that the primary source was a Danish swine herd [38]).

The most important reservoir for human *Campylobacter* infections is poultry. Endtz et al. [39] observed that the emergence of fluroquinolone resistant *Campylobacter jejuni* infections in humans in the Netherlands coincided with the introduction of enrofloxacin, a fluoroquinolone for poultry therapy in spring 1987. Enrofloxacin and ciprofloxacin, introduced in October 1988 for human therapy in the Netherlands, are fully cross-resistant to ciprofloxacin. Experimentally, it was shown that in flocks only colonised with ciprofloxacin susceptible *C. jejuni* resistant mutants emerged after a therapy with enrofloxacin [40]. In Great Britain, enrofloxacin was registered for veterinary use in 1993 and in that year 14% of *C. jejuni* isolated from poultry carcasses imported from the Netherlands were fluoroquinolone resistant and only 1% from locally

raised broilers [41]. In 1997, the percentage of fluoroquinolone resistant *C. jejuni* from English broilers had approached a continental level — 10%. Transfer of chloramphenicol resistant *Yersinia enterocolitica* strains from animals to humans has been described by Perez Trallero [42].

3.2. Disturbance of colonisation resistance

Another aspect of the usage of antibiotics is disturbance of the colonisation resistance (CR) or the intestinal flora of animals exposed to certain antibiotics [43,79]. In the case of a reduced colonisation resistance not only the minimal infection or colonisation dose of pathogenic or resistant bacteria is considerably lower, but animals excrete these bacteria in higher numbers and over a larger period of time compared with animals with an intact colonisation resistance. This not only enhances dissemination of salmonellae or resistant bacteria within a group of animals, but also increases the contamination of carcasses with these bacteria during slaughter. This effect has been clearly demonstrated for most broad-spectrum antibiotics [44] and for certain APE, avoparcin [45–47] and to a lesser extend for virginiamycin and tylosin [48,49]. Avilamycin and bacitracin seem not to disturb the CR in the dosages used for growth promotion [50–54]. Flavomycin has been shown to provide a certain protection against *Salmonella* infections [55].

3.3. 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 increases. These bacteria not only constitute an enormous reservoir of resistance genes for (potentially) pathogenic bacteria, but also the level of resistance in the endogenous flora is considered to be a good indicator for the selection pressure exerted by antibiotic use in that population [56] and for the resistance problems to be expected in pathogens [57]. Resistant bacteria from the intestinal flora of food animals contaminate carcasses of slaughtered animals like zoonotic bacteria 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 resistance 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 is high in hospitals. Emergence of new resistances due to the acquirement of new genes or gene clusters like the *Van*A-gene cluster is not likely to occur in hospitals but must have been introduced into hospitals once. Therefore, healthy individuals in the community outside hospitals harbour not only a reservoir of resistant bacteria and resistant genes, but are considered to be a suitable population to study the possibility of transfer of resistant bacteria or resistance genes from animals to humans.

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

Population	*N*	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

Corpet showed that the prevalence and degree of resistance in faecal *E. coli* flora of humans, who used only sterilised food, decreased significantly [58]. Nijsten found significantly more resistant *E. coli* in the faecal flora of pig farmers than in faecal samples from pig slaughterers and (sub) urban residents [59,60]. But the personal antibiotic usage of the farmers was much higher than that of urban residents.

Comparison of the prevalence of ciprofloxacin resistant *E. coli* in faecal samples of turkeys and turkey farmers with pig and pig farmers, strongly indicated transfer of ciprofloxacin resistant *E. coli* strains from turkeys to turkey farmers (Table 4) [61]. 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 in both animals species used extensively like furazolidon in the past. 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 after *Xba*I digestion. None of the turkey farmers and urban residents in this study had used antibiotics 3 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 [16]. 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 usage of furazolidone, also an antibiotic against which transferable resistance is of no importance, 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 transfer of resistant strains from animals to humans. The extent of transfer seems to be connected 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 were also isolated from a turkey farmer and from his turkeys, which were not only identical using PFGE after *Sma*I digestion, but also had a *Van*A gene with a unique mutation [62]. This again strongly indicates transfer of resistant strains from animals to humans. Moreover, in Sweden not only were no VRE found in the faecal flora of healthy humans and animals, but also no VRE could be detected in stool samples of healthy volunteers after taking a course of vancomycin orally [63]. In Belgium, in a similar experiment, all volunteers, in which no VRE were found in their stool samples before the study, became positive [64,65]. This is in agreement with the results of Quednau et al., who where able to isolate VRE from Danish, but not from Swedish meat (products) [43]. Recently, a significant decrease in the prevalence of VRE isolated from poultry meats within 2 years after banning of avoparcin in the respective countries was observed in Germany and Italy [66,67]. The percentage of positive poultry meats in Italy decreased from 15% in March 1997 to 8% in October 1998. Moreover, the prevalence of colonisation of healthy persons with VRE in Germany decreased from 12% in 1994 to 3% in 1997. These results indicate the selective pressure by glycopeptides for VRE in poultry and underline the role of poultry meats for the dissemination of resistant bacteria and resistance genes from poultry to healthy humans in the community.

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

In 1976, Levy had observed in a prospective study that in chickens fed with tetracycline, there was transfer of 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 *tet*Q was observed by Nikolich and Shoemaker. They found identical *tet*Q genes in host specific intestinal flora bacteria, *Bacteroides* spp. and *Prevotella intermedius* from humans and *P. ruminicola* from bovines [69,70].

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 DDR nourseotricin, a streptotricin antibiotic was introduced as an APE for pigs. Streptotricin antibiotics have not been used in human medicine and do not show cross-resistance with other antibiotics. Within 1 year of its introduction, resistance to nourseotricin occurred in faecal *E. coli* from pigs fed with this antibiotic. The resistance genes were located on a transposon Tn 1825 and within 2 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 has never been found.

Other examples of the dissemination of resistance genes from animals to humans are the dissemination of the *aac*C4 gene (apramycin resistance) and *hph*B gene (hygromycin resistance) from animals to human bacteria. Despite the fact that these antibiotics are only used in animals, these genes, which are co-transferred 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].

5. Conclusions

In animals as in humans the use of antibiotics not only causes 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 animals 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, greater the number of resistant bacteria in the intestinal flora, greater is the likelihood that genes encoding resistance will be transferred to (potentially) pathogenic bacteria and disseminated into the environment and from animals to foods of animal origin. In this respect one might consider the resistance observed in zoonotic and nosocomial pathogens to be just the tip of the iceberg. As bacteria from human flora can not only cause infections in immunocompromised hosts, but are also considered to be an important reservoir of resistance genes for human 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 a normal blood pressure and a low serum cholesterol level are public health

goals [59]. Despite the fact that it is not yet clear 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 definite factor. Because we are now encountering in human medicine some microorganisms that are so multiresistant that it is difficult and may be soon impossible to fight these with the clinically available antibiotics, every source of resistance must be controlled as well as possible. Therefore, a low level of resistance in the intestinal flora of food animals should be thought of as a distinguishing safety mark for food animals [15,76]. 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 of 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 development of new vaccines. If antibiotics have to be used, the use of small spectrum molecules should be preferred and there should be a sensible veterinary antibiotic policy [77]. Discontinuing the practice of routinely adding APE to animals feeds would reduce the amounts of antibiotics used for animals in the EU by at least 30% and in some countries even by 50%. In this case the public health risks should be weighted against the economical profits, and/or alternative to APE such as pre- and probiotics should be developed. The Swedish have shown that modern and profitable animal husbandry without APE is feasible [78]. Last but not least the decrease in the prevalence of VRE in poultry, in poultry meats and in humans after abolition of avoparcin use in animals shows that intervention measures may be effective [23,66,67].

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