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**COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE
(CVMP)**

**PUBLIC STATEMENT ON THE USE OF (FLUORO)QUINOLONES IN FOOD-PRODUCING
ANIMALS IN THE EUROPEAN UNION: DEVELOPMENT OF RESISTANCE AND
IMPACT ON HUMAN AND ANIMAL HEALTH**

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MANDATE

The Scientific Advisory Group on Antimicrobials (SAGAM) was mandated to give advice to the CVMP on the need to exercise certain control on those classes of compounds of greater importance to human medicine e.g. fluoroquinolones and 3rd and 4th generation cephalosporins.

This document only discusses (fluoro)quinolones.

INTRODUCTION

The introduction of antimicrobial agents in human medicine and veterinary medicine has been one of the most significant medical achievements of the 20th century. The first antimicrobial agents were introduced in the 1930's, and a large number of new compounds were discovered in the following decades. However, shortly after the introduction, resistance began to emerge. In all known cases emergence of antimicrobial resistance has eventually followed the introduction of a new antimicrobial compound. Therefore, antimicrobial resistance poses a risk to human and animal health and should be taken seriously as it reduces the efficacy of antimicrobials in the treatment of infectious diseases in both animal and human medicine.

In animal production systems with high density of animals or poor biosecurity, development and spread of infectious diseases is favoured, which leads more frequently to antimicrobial treatment and increases the need for prevention of those diseases. One approach should be to reduce the occurrence of food-borne pathogens as such. When the numbers of *Salmonella* and *Campylobacter* are reduced, transmission of fluoroquinolone-resistant pathogens will consequently be lowered. Hence, Good Agricultural Practice (GAP) must have a high priority. The frequent and imprudent use of antibiotics will provide favourable conditions for selection, spread and persistence of antimicrobial-resistant bacteria. Some of these bacteria are capable of causing infections in animals, and if zoonotic, also in humans. Bacteria of animal origin can also be a source for transmission of resistance genes to human and animal pathogens. Antimicrobial resistant bacteria can have human health consequences due to the increased occurrence of infections with resistant bacteria during and after treatment with antibiotics these bacteria are resistant to as reported by Barza and Travers (2002) for *Salmonella* infections. Also treatment failures and increased severity of infections can be a consequence (Holmberg et al. 1987). Emergence of antimicrobial resistance in animals may have serious consequences on animal health and welfare. They depend on the severity of the infectious disease but lack of the efficacy of the treatment may lead to considerable animal suffering and also economical losses.

International bodies (e.g. WHO, OIE) and regulatory authorities have concerns on development of antimicrobial resistance in human and animal pathogens including zoonotic organisms and commensal bacteria and in particular for certain classes of antimicrobials as fluoroquinolones. The extent of the use of (fluoro)quinolone-containing products in animals is not well known and information on resistance development is not yet available from all EU countries. The information available so far indicates that nalidixic acid resistance as well as fluoroquinolone resistance is in some regions of the EU commonly present and increasing.

Fluoroquinolones represent a class of antimicrobials which is most important in the treatment of severe and invasive infections in humans and animals and are therefore of special interest for public and animal health. Both older and newer generations of quinolones have an impact on resistance, and therefore the term (fluoro)quinolones is used unless there is a need to refer to a specific molecule or old quinolones are not addressed.

OBJECTIVE

The objective of this document is to critically review recent information on the use of (fluoro)quinolones (older generation quinolones as well as fluoroquinolones) in food-producing animals other than in aquaculture and honey production in the EU, its effect on development of resistance to this category of antimicrobial agents in bacterial species that are of importance for human and animal health, and the potential impact on human and animal health.

USE AND IMPORTANCE OF FLUOROQUINOLONES FOR TREATMENT OF INFECTIONS IN FOOD-PRODUCING ANIMALS

The first older generation quinolones (oxolinic acid and flumequine) were licensed for use in food animals at the beginning of the 1980's and the first fluoroquinolone (enrofloxacin) during the late 1980's and early 1990's. Since then additional fluoroquinolone molecules have been authorised and a number of different veterinary medicines are now available on the market.

Fluoroquinolones are very potent antimicrobials and active against a wide range of pathogenic organisms and well distributed in the body after administration. This class of antimicrobials has a therapeutic effect on most infections in different organs or tissues. Although it is rare that fluoroquinolones are the only available agent for treatment of a specific infectious disease, fluoroquinolones are important alternative medicinal products for a veterinarian to have as option for treatment. Fluoroquinolones have a unique mechanism of action not related to conventional antimicrobials, and therefore their efficacy should be retained as long as possible.

It is difficult to obtain good information about the consumption of antimicrobial agents for food-producing animals although the situation is slowly improving. Exact figures are still rare and estimates are only available for a few countries. Furthermore, data from countries are generally compiled for all animal species including dogs and cats, but only a few datasets are separated into the different animal species.

The most recent data on use of (fluoro)quinolones are compiled in table 1. As the number of animals produced in the different countries varies considerably, information on the volume of animals slaughtered is given for reference. It is to be observed that the volume slaughtered will include animals imported live for slaughter, and exclude animals exported live for slaughter (but reared within the country).

Table 1. Sales of (fluoro)quinolones (tonnes active substance) and production of meat in some EU Member States with ongoing drug use monitoring programmes^a. Data from some Member States include also the use in fish.

Country	Sales of antimicrobials (metric tonnes)		Production of meat (metric tonnes slaughtered)			
	Fluoro- quinolones	All quino- lones	Beef and Veal	Pork	Poultry	Sum, production
Czech Republic	0.8	1	103775	409102	215802	728679
Denmark	0.1	0.1	147600	1762000	199994	2109594
Finland	< 0.1 ^b	< 0.1	95830	193222	83730	372782
France	3.6 ^b	20.7	1631000	2321000	2010700	5962700
Netherlands	0.3 ^c	5.0 ^b	364000	1250000	564000	2178000
Portugal	3.0	3.8	118524	315141	229335	663000
Sweden	0.2 ^b	0.2	136300	287500	99850	523650
United Kingdom	1.4 ^b	1.4	687000	690000	1569987	2946987

^a Data are for year 2003 except antimicrobial sales figures from France that are from 2002 and for beef and veal and Pork figures from Portugal that are from 2004. Information compiled from: AFSSA 2004, DANMAP 2003, FINRES–Vet 2002-2003, INFARMED (not published), MARAN 2003, SVARM 2003, VMD 2004, Czech Republic database of Institute for State Control of Veterinary Biologicals and Medicaments 2005 (Bulletin of Institute for the State Control of Veterinary Biologicals and Medicaments 2005), and for production of meat FAOSTAT 2005 and Instituto Nacional de Estatística Portugal (INE).

^b Includes dogs and cats.

^c Broilers only.

There are clear differences in the amount of (fluoro)quinolones used in different countries (Table 1). These data are difficult to interpret as e.g. animal species are not differentiated in the data. If the consumption figures are related to the amount of meat produced in the countries (Table 1), differences can be seen which may indicate differences in the consumption patterns between countries. National actions can have an effect on the use patterns of fluoroquinolones. This has been documented in Denmark and the Netherlands.

(Fluoro)quinolones for food-producing animal use have been authorised in the EU via the national procedure, mutual recognition or centralised procedure. The number of authorised products containing (fluoro)quinolones varies between different EU countries. Moreover the indications for use of the products are not the same in all countries and marketing of the products can differ between countries.

Currently there is no harmonised approach on prudent use of (fluoro)quinolones in animals in the different Member States. In some marketing authorisations in the EU, special precautions for use have been added to the Summary of Product Characteristic (SPCs) of fluoroquinolone products. Prudent use guidelines on the use of antimicrobials for animals have been published in many countries but most are on a general level and (fluoro)quinolones are not specifically mentioned. Some national guidelines however give specific recommendations also for the use of fluoroquinolones (e.g. Anon. 2003). FVE guideline on prudent use (1999) is at a general level and states "where an appropriate narrow spectrum agent is available, it should be selected in preference to a broad spectrum agent".

RESISTANCE

Antimicrobial resistance among human pathogens which is not related to veterinary use

A detailed account of antimicrobial resistance in human pathogens, and its relation to human use is outside the scope of this document, but it is important to stress that most of the problems with resistance in human medicine are correlated to use of antimicrobials in humans.

There are significant variations in use in human medicine of total amounts as well as in different classes of antimicrobials between countries in Europe (European Commission 2005). Regarding fluoroquinolones, outpatient use in 2002 in Europe varied between countries with a factor of 21.2 (Goossens et al. 2005).

There are also geographical differences in the proportion of resistance to antimicrobials, including fluoroquinolones, among common human pathogens (EARSS 2005), and there is generally a correlation between human use and resistance (Goossens et al. 2005). This is true also for hospital settings, for example both the overall use of fluoroquinolones and prior patient specific use correlate to the risk of a patient acquiring a nosocomial infection with *Pseudomonas aeruginosa* being non-susceptible to fluoroquinolones (Ray et al. 2005).

Globally, fluoroquinolone resistance is increasing among major nosocomial pathogens such as *Pseudomonas aeruginosa* and methicillin resistant *Staphylococcus aureus* (MRSA), as well as in major causes of community acquired infections such as *Streptococcus pneumoniae* and *Neisseria gonorrhoeae* (GAARD 2005). For these examples, there is no demonstrated or perceived link to use of (fluoro)quinolones for animals. But resistance is also an increasing problem for enteric infections with zoonotic agents (*Salmonella*, *Campylobacter*) (Engberg et al. 2001) and for those infections, the link to veterinary use of (fluoro)quinolones is well documented, as discussed further in this document.

Mechanism of (fluoro)quinolone resistance and interpretation of susceptibility tests

(Fluoro)quinolones inhibit the activity of the DNA gyrase and in most bacterial species resistance is due to mutations in the gyrase or topoisomerase genes. In *Enterobacteriaceae* resistance to fluoroquinolones is most commonly acquired by mutations in two steps. One mutation in the *gyrA* gene mediates full resistance to first generation quinolones such as nalidixic acid and flumequine and reduced susceptibility to fluoroquinolones. A second mutation in either *gyrA* or *gyrB* genes mediates 'full resistance' to fluoroquinolones.

Recently in *Klebsiella pneumoniae* and *E. coli* a plasmid mediated resistance mechanism (*qnr*-gene) has been described. It has emerged in the US, China (Martinez et al. 1998, Wang et al. 2003, Tran et al. 2002), but more recently this gene was detected in *Enterobacter cloacae* in 5 hospitals in The Netherlands (Pauw et al. 2006) linked to resistance to third generation cephalosporins, gentamicin and streptothricin. This resistance has recently been reported from *Salmonella enteritidis* isolates obtained from patients in Hong Kong, where it was found to be located on transferable plasmids (Cheung et al. 2005). Thus, we must expect that this mechanism also will emerge in the food animal population in Europe. The typical phenotype of *qnr*-positive *Enterobacteriaceae* is reduced susceptibility to fluoroquinolones (Ciprofloxacin MIC 0.25 – 0.5 mg/l) and susceptibility to nalidixic acid (MIC 16 mg/l).

The Breakpoint Minimum Inhibitory Concentration (MIC) is the threshold above which a particular pathogen is unlikely to respond to the specified antimicrobial agent. Breakpoints can be used for clinical or epidemiological purposes.

The clinical breakpoint should take the behaviour of the drug following administration into account, and it is assumed that if an isolate shows a MIC below the allocated clinical breakpoint for the pathogen, then a response can be predicted if the drug is dosed as recommended, and there are no other factors to affect the outcome. Conversely, a MIC found to be above the clinical breakpoint indicates resistance, and a poor prognosis for the treatment.

A breakpoint for epidemiological purposes takes into account the MIC distribution pattern determined for bacteria populations. It enables identification of two or more populations that can be differentiated by the presence or absence of resistance factors. The wild-type (WT) “susceptible” subpopulation has the MIC profile before any resistance has developed or has been acquired, and its distribution can be differentiated from the “resistant” subpopulation. This epidemiological breakpoint is defined as: epidemiological cut-off value for the WT distribution (also referred to as microbiological breakpoint) and is not necessarily associated with therapy failure.

Clinical breakpoints for resistance generally only define isolates with MICs indicating two mutations as resistant. Thus, the European Committee on Antimicrobial Susceptibility Testing (EUCAST), a standing committee on antimicrobial susceptibility testing under the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) has defined a clinical breakpoint for resistance to ciprofloxacin in *E. coli* as >1 mg/l (<http://www.srga.org/eucastwt/MICTAB/index.html>). The Clinical Laboratory Standards Institute in the US (CLSI; formerly National Committee for Clinical Laboratory, NCCLS) in its current standard recommends a breakpoint for resistance to ciprofloxacin of ≥ 4 $\mu\text{g/ml}$ (NCCLS 2004). In notes to the breakpoints, EUCAST states ‘there is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by *Salmonella* spp. with low-level fluoroquinolone resistance (MIC >0.064 mg/l). The available data relate mainly to *S. Typhi* but there are also case reports of poor response with other *Salmonella* species’ and CLSI, in a supplement (CLSI 2003) mentions that ‘fluoroquinolones-susceptible strains of *Salmonella* that are resistant to nalidixic acid may be associated with clinical failure’.

When monitoring for resistance to fluoroquinolones nalidixic acid should be used as a marker for decreased susceptibility caused by chromosomal mutations because this is more indicative of emerging resistance in *Enterobacteriaceae*. Because of the recent awareness of emergence of plasmid mediated quinolone resistance in *Enterobacteriaceae*, fluoroquinolones (such as ciprofloxacin) with epidemiological cut-off values should be used (EUCAST) besides nalidixic acid in order to detect acquired resistance optimally.

In *Campylobacter* high-level fluoroquinolone resistance is mainly to be due to mutations in the *gyrA* gene encoding part of the A subunits of DNA gyrase (for review see Aarestrup and Engberg 2001). In contrast to the situation for *Enterobacteriaceae* one single mutation causes full resistance to both fluoroquinolones and nalidixic acid and thus, interpretation of resistance is less problematic because clinical breakpoints for *Enterobacteriaceae* and epidemiological cut off values for *Campylobacter* are generally very similar for nalidixic acid or fluoroquinolones.

Selection for resistance in food borne pathogens when using (fluoro)quinolones in food-producing animals

Emergence and increases in resistance following introduction of fluoroquinolones

Field bacterial isolates have only rarely been tested for susceptibility to new antimicrobial agents prior to the introduction. Nonetheless, some observations on the susceptibility patterns before the introduction and on the emergence of resistance after the introduction of new antimicrobial agents into veterinary medicine have been made.

Fluoroquinolones were introduced for veterinary use in different countries around the world during the late 80'ties and the beginning of the 90'ties. This introduction and subsequent use has been followed by the emergence of antimicrobial resistance in bacteria of food-producing animals and subsequently spread of resistant zoonotic bacteria to humans (Engberg et al. 2001). The reason is that food-producing animals, especially poultry, very commonly have campylobacters in high numbers as commensals in their gastro-intestinal flora. During treatment of infectious diseases like colibacillosis, resistant mutant are readily selected. The first reported study is from The Netherlands, where water medication with the fluoroquinolone enrofloxacin in the poultry production was followed by an emergence of fluoroquinolone resistant *Campylobacter* strains among both poultry and humans (Endtz et al. 1991). Retrospectively Endtz et al. determined that in the four years before the introduction of fluoroquinolones in poultry fluoroquinolone resistance was absent in *Campylobacter* strains in The Netherlands. Since then several studies worldwide have documented an increase in the occurrence of resistance to fluoroquinolones among *Campylobacter* from food-producing animals and humans following the use of fluoroquinolones for the treatment of infections in food-producing animals (reviewed in Engberg et al. 2001, Lucey et al. 2002, Nachamkin et al. 2002, Hein et al. 2003, Gaudreau and Gilbert, 2003). In Australia where fluoroquinolones are not licensed for use in poultry *C. jejuni* has remained susceptible to fluoroquinolones (Unicomb et al. 2006).

The relation between usage of fluoroquinolones and development of resistance is complex, and therefore it may be difficult to draw firm conclusions. The microbiological methods used for isolation and identification of *Campylobacter* have varied in the different studies published. Since the nineties there has been widespread use of fluoroquinolones both in veterinary and in human medicine, indicating that also usage in humans may have contributed to resistance as has been pointed out in several publications (Bywater and Casewell 2000, Vogel 2002, Radostits 2004, Phillips et al. 2004). However it needs to be emphasised that in humans campylobacters are only present in the patients gut during an infection with the organism. *Campylobacter* carriers do not occur and human-to-human transmission is rare. In humans fluoroquinolone resistant mutants will be selected only during treatment of campylobacteriosis with fluoroquinolones. Since in human therapy fluoroquinolones are predominantly used for other infectious diseases, its relative contribution to the resistance levels of *C. jejuni* will be less significant.

Similar trends have been observed for several *Salmonella* serovars. In Germany, an increase in the incidence of strains of *Salmonella* that are resistant to nalidixic acid was observed after the licensing of enrofloxacin (Malorny et al. 1999). Simultaneous increase in resistance was observed in France among isolates from animals and humans, and the same clones were observed among the different reservoirs (Heurtin-Le Corre 1999). Also in Spain the occurrence of nalidixic acid resistance among *Salmonella* causing infections in humans increased from less than 0.5% before 1991 to 38.5% in 2003 in one study (Marimon et al. 2004) and from around 6 to 15% in 1991 to 40 to 85% in 2001 in another study (Guerra Santos and Rotger 2004). In the United Kingdom substantial increases in resistance to nalidixic acid in *Salmonella* Hadar and *Salmonella* Virchow, and in multiresistant *Salmonella* Typhimurium DT104 followed the authorisation for veterinary use of enrofloxacin in 1993 and danofloxacin in 1996 (Threlfall et al. 1997). In Taiwan a number of studies have shown the emergence of fluoroquinolone resistance in *Salmonella* from pigs and the subsequent spread of those isolates to humans (Su et al. 2001, Chiu et al. 2002, Hsueh et al. 2004).

In Table 2, data on resistance to nalidixic acid or flumequine in zoonotic organisms isolated from animals in different European countries are given. These data are cited from a report of ARBAO II (Antimicrobial resistance in bacteria of animal origin, a EU concerted action via FAIR) and are generally from year 2002 (Anon. 2004). For nalidixic acid, the breakpoints applied are comparatively similar. Despite that inclusion criteria and number of isolates vary substantially between countries, the figures indicate that the proportion of isolates showing resistance to nalidixic acid or flumequine (and hence for *Salmonella* decreased susceptibility to fluoroquinolones) differ considerably between countries. Higher figures are found among *S. Enteritidis* from poultry.

Table 2. Proportion resistance (%) to quinolones^a among *Salmonella* and *Campylobacter* from food-producing animals (Data from ARBAO II, Anon. 2004).

Country	Pathogen and percent reported resistance to quinolones				
	Salmonella		<i>C. coli</i>	<i>C. jejuni</i>	
	<i>S. Typhimurium</i> , pigs	<i>S. Enteritidis</i> , poultry	Pigs	Cattle	Poultry
Austria	0	2			
Belgium	6	0			
Denmark	<1	23	8	11	0
England and Wales	8	0	17	0	
France	0		20		36
Germany	4	14			8
Greece		44			
Netherlands	3	3	11		38
Norway					0
Poland		8			
Sweden			18	2	0
Switzerland	0		26	5	12

^a Resistance to nalidixic acid or flumequine. In the ARBAO database breakpoints were not standardised so the results might be affected by differences in the interpretation criteria between countries.

In several of the ongoing national resistance monitoring programmes, resistance among commensals isolated from healthy animals at slaughter is monitored. In Table 3, figures on resistance among *E. coli* from healthy pigs and broilers are given (for references see table subscript). The programmes from which data have been compiled have similar sampling strategies and methodology for testing. The distribution of MICs of all tested isolates are reported (except ITAVARM where disk diffusion results are reported), which further facilitates comparisons. The apparent prevalence of resistance to quinolones, but also resistance using the clinical breakpoint of CLSI for enrofloxacin varies substantially between the different countries, and the variations are most obvious in poultry.

Table 3. Proportion resistance (%) to fluoroquinolones and flumequine or nalidixic acid among *Escherichia coli* from pigs and broilers sampled at slaughter^a.

Origin and quinolone	Break-point (mg/l)	Country and percent resistance							
		Austria	Denmark	Finland	France	Italy	Netherlands	Norway	Sweden
Pigs		(n=134)	(n=317)	-	(n=304)	(n=255)	(n=155)	(n=187)	(n=303)
Fluoroquinolone ^b ,	>2	2	0	-	0	<1	0	0	0
Nalidixic acid or flumequine	>16 or >4	8	2	-	3	9	0	<1	1
Broilers		(n=140)	(n=138)	(n=300)	(n=308)	(n= 258)	(n=165)	(n=141)	(n=306)
Fluoroquinolone ^b ,	>2	3	0	0	3	11	3	0	0
Nalidixic acid or flumequine	>16 or >4	54	10	2	28	50	35	1	5

^a Source of information: AFSSA 2004, DANMAP 2003, FINRES 2002-2003, ITAVARM 2003, MARAN 2003, NORM/NORMVET 2002, REMOST 2003, SVARM 2003. Year of investigations: Austria (Steiermark) 2003, Denmark 2003, France 2000, Finland 2002-2003, Italy 2002-2003, The Netherlands 2003, Norway 2002, Sweden 2002 for broiler and 2003 for pigs.

^b Enrofloxacin or ciprofloxacin

Animal experiments to study the development of resistance

Experimental studies can be performed under well-controlled conditions and are very useful in giving confirmatory information on what can happen under given circumstances. Several experimental studies have shown that resistance will develop in the intestinal and the skin flora when animals receive antimicrobials (Smith 1967, Christie et al. 1983, Hinton et al. 1985, 1986, Kaukas et al. 1987, Jacobs-Reitsma 1994, Aarestrup and Carstensen 1998).

For fluoroquinolones Jacobs-Reitsma (1994) reported that giving enrofloxacin to poultry would select for fluoroquinolones resistance in *Campylobacter*. Similarly, van Boven et al. (2003) found that administration of 50 ppm enrofloxacin in drinking water led to the immediate emergence of fluoroquinolone resistant *Campylobacter jejuni* isolates. McDermott et al. (2002) found the same using a 5 day treatment with both enrofloxacin and sarafloxacin in the USA. Delsol et al. (2004) also found that a single 5 days treatment of pigs lead directly to the emergence and persistence of fluoroquinolone resistance in *Campylobacter coli* for at least 5 weeks.

Wiuff et al. (2003) found that in pigs infected with a mixture of susceptible and nalidixic acid resistant *Salmonella* a 3-day treatment with enrofloxacin would select for nalidixic acid resistant strains. This study also found that increasing the dose would reduce the selection for resistance. In another study it was observed that a 5-day enrofloxacin treatment on *Salmonella enterica* serotype Typhimurium DT104 in a pig model failed to eradicate nalidixic acid susceptible *S. Typhimurium* DT104, which continued to be isolated up to 35 days after treatment (Delsol et al. 2004). Furthermore, the treatment positively selected for already nalidixic acid resistant *S. Typhimurium* DT104 strains which remained present during a 10 days withdrawal time for enrofloxacin.

Epidemiology of food borne infections by antimicrobial resistant bacteria

In the developed countries most human infections with *Campylobacter* and non-typhoidal *Salmonella* are food borne. It is generally agreed that the main reservoir of these bacteria are food-producing animals and that the main source of infections are animal products (Anderson et al. 2003, Coyle et al. 1988, Humphrey 2000). In the United States 95% of the 1.4 million cases of *Salmonella* infections estimated to occur annually are attributed to food-borne transmission (Meng and Doyle 1997).

Although usage in humans may contribute to resistance in *Salmonella*, antimicrobial resistant *Salmonellas* isolated from human infections most likely have acquired resistances while living in the food producing animals (Bezanson et al. 1983, Cohen and Tauxe 1986, Holmberg et al. 1984, Spika et al. 1987, Tacket et al. 1985, Thornton et al. 1993, Glynn et al. 1998, Mølbak et al. 1999, Aarestrup and Wegener 1999, Threlfall 2002, White et al. 2002). Epidemiological and microbiological studies have also demonstrated that nalidixic acid resistant *Salmonella* were selected and disseminated in the animal production and subsequently spread to and cause infections in humans (Angulo et al. 2000, Chiu et al. 2002, Heurtin-Le Corre et al. 1999, Hsueh et al. 2004, van Pelt et al. 2003, Mølbak et al. 1999, Walker et al. 2000). Dissemination of *Salmonella* including (fluoro)quinolone resistant *Salmonella* isolates is not necessarily related to antimicrobial usage. International trade and human travel have disseminated resistant *Salmonella* isolates worldwide.

Sound scientific evidence of the source of fluoroquinolone resistant campylobacters in human infections is more difficult to achieve. Reliable and reproducible typing studies on *Campylobacter* are difficult to perform, thereby making it difficult to trace the spread of individual clones. Epidemiological studies have pointed to poultry products as the main reservoirs of fluoroquinolone resistant *Campylobacter* (Smith et al. 1999, Anon. 2002, Kassenborg et al. 2004). Furthermore, similar genotypes have been found among fluoroquinolone resistant *Campylobacter* from poultry and infections in humans, despite the multi-clonal nature of the organism (Wu et al. 2002).

As far as *E. coli* is concerned, it has until now been the general belief that *E. coli* from animals and humans belong to different populations and that animal strains of *E. coli* usually do not infect humans, with the important exception of *E. coli* O157:H7, and other zoonotic Shiga toxin producing *E. coli* serotypes (Aarestrup and Wegener 1999). In Spain it has previously been reported that quinolone resistance emerged simultaneously in *E. coli* from food-producing animals and infections in humans (Garau et al. 1999). A recent study from the US has already pointed a high degree of genetic relatedness between human and animal *E. coli* (Johnson et al. 2005). The potential zoonotic origin of these *E. coli* infections is still quite uncertain and further studies are needed to clarify the matter.

Impact of infections with (fluoro)quinolone resistant food borne zoonotic bacteria to human health

Antimicrobial resistant bacteria can have human health consequences either due to the occurrence of infections that would otherwise not have occurred (excess infections) or due to treatment failures and increased severity of infections (FAO/OIE/WHO 2003).

The use of antimicrobial agents in humans could also temporarily disturb the intestinal microflora placing such individuals at increased risk of infections with intestinal pathogens. Taking an antimicrobial agent for e.g. respiratory infections increases the risk of becoming infected with intestinal pathogens resistant to that antimicrobial agent. Barza and Travers (2002) estimated that in the USA resistance to antimicrobial agents results annually in an additional 29,379 *Salmonella* infections, leading to 342 hospitalisations and 12 deaths, and an additional 17,668 *Campylobacter jejuni* infections, leading to 95 hospitalisations. Estimates of the excess infections are lacking in the EU.

For uncomplicated acute infectious gastroenteritis antibiotic treatment is not indicated in human medicine. In some European countries it is even considered contra-indicated for treatment of uncomplicated non-typhoidal salmonellosis. The reason is that antibiotic treatment induces prolonged excretion of *Salmonella*'s (carriers) and increased frequency of relapses (Sirinavin and Garner, 2004). For patients at risk (e.g. immunocompromised, severely infected and elderly) fluoroquinolones are considered first choice drugs. For infections with (fluoro)quinolone resistant *Salmonellas* alternative antimicrobials are cephalosporins (3rd or 4th generation).

Holmberg et al. (1987) found that infections with multi-drug resistant *Salmonella* were associated with a higher death rate than infections with susceptible isolates. Lee et al. (1994) reported increased hospitalisation rate and longer illness for resistant compared to susceptible *Salmonella*. Martin et al. (2004) reported that patients infected with multiple resistant *Salmonella* Typhimurium were more likely to be hospitalised compared to patients infected with susceptible isolates. Helms et al. (2002) reported that patients infected with nalidixic acid resistant (MIC > 0.125 to ciprofloxacin) isolates were five times more likely to die within two years after infection compared to patients infected with susceptible isolates. A later study conducted by the same research group found a 3.15 times increased mortality when infected with a nalidixic acid resistant *Salmonella* Typhimurium compared to infections by susceptible isolates (Helms et al. 2004). Information on treatment regimens in these cohorts was missing.

If indicated for treatment of *Campylobacter* infections in humans, macrolides are considered the first choice drugs. Resistance to macrolides in *Campylobacter* species is still relatively rare and predominantly present in *C. coli*. For *Campylobacter* it has been reported that infections with isolates resistant to (fluoro)quinolones and macrolides are associated with longer duration of diarrhoea (2 to 3 days) and hospitalisations and with increased mortality (Marano et al. 2000, Smith et al. 1999, Friedman et al. 1998, Engberg et al. 2004, Helms et al. 2005).

For empiric treatment of community acquired acute infectious gastroenteritis fluoroquinolones are considered among the first choice antimicrobials. Because resistance to fluoroquinolones may be present in the bacterial pathogens (*Salmonella*, *Shigella*, *Yersinia* and *Campylobacter*), alternative treatments like cephalosporins, erythromycin or azithromycin exist (Yates, 2005). For susceptible organisms treatment with fluoroquinolones is considered effective in reducing the disease length if the treatment starts early in the infection.

Animal health consequences resulting from fluoroquinolone resistant bacteria

Fluoroquinolones are highly potent bactericidal substances well absorbed after oral administration, have a long elimination half-life and widespread distribution throughout the body, which make them attractive to be used e.g. in herd treatment of food-producing animals. Development of resistance may not have been expected by the early users. However, resistance to fluoroquinolones emerged and increased among several bacterial species pathogenic for food-producing animals following the introduction of enrofloxacin (Aarestrup et al. 2000, MARAN 2003). No resistance was observed prior to this introduction and the same methods for isolation, identification and susceptibility testing were used before and after the introduction of enrofloxacin.

If (fluoro)quinolone resistance develops for an animal pathogen, this may result in therapeutic failure, including mortality. Unfortunately little data exist on the animal health or welfare problems associated with lack of treatment efficacy due to antimicrobial resistance during (fluoro)quinolone treatment. Bosch and Hartman (1993) described an outbreak of *S. Typhimurium* infection in veal calves with a unique pattern of resistance. The strain was multidrug resistant to most conventionally used antibiotics and also resistant to enrofloxacin. The authors reported that antibiotic resistance and management factors resulted in a mortality exceeding 90%. Data on the occurrence of fluoroquinolone resistance among different animal pathogens from 2002 were collected and published (Anon. 2004, table 4). The data were compiled from laboratories using different breakpoints and thus, any conclusions have to be drawn with care. Furthermore the information was based on clinical samples and therefore likely to be biased due to possible use of antimicrobial therapy before sampling.

Table 4. Proportion resistance (%) to fluoroquinolones among animal pathogens from food-producing animals (data from ARBAO II, Anon. 2004).

Country	Pathogen and percent reported resistance to fluoroquinolones					
	<i>A. pleuropneumoniae</i>	<i>E. coli</i>			<i>P. multocida</i>	<i>M. haemolytica</i>
	Pigs	Cattle	Poultry	Pigs	Cattle	Cattle
Belgium		35		3		
Denmark	0	1	0	0	0	
England and Wales	4	< 1	3	8	0	0
Finland				11		
France	0	31	5	5	5	5
Germany		2			1	2
Italy		22	4			
Latvia				44		
Netherlands					0-1	2-6
Norway			2	0		
Poland	1					0
Portugal				76		
Spain		12		16		
Sweden	0	1		3	< 1	
Switzerland						

Fluoroquinolones are effective in the treatment of serious infections like septicaemia, gastroenteritis and respiratory diseases caused by susceptible Gram-negative bacteria. They are also used to treat urinary tract and skin infections, and soft-tissue infections caused by Gram-negative or some Gram-positive aerobic bacteria. They are effective for the treatment of Mycoplasma infections, and due to their ability to penetrate phagocytes, they have potential for the treatment of infections caused by atypical bacteria such as mycobacteria, *Chlamydia* spp., *Ehrlichia* spp., or *Rickettsia* spp. Documentation about their efficacy to treat all these infections is however not complete. For many of the listed indications, satisfactory alternative treatments are available. The authorised dosages of fluoroquinolone preparations have not always been determined on the base of the pharmacokinetic and pharmacodynamic properties, maximising the clinical efficacy and decreasing the selection of resistance. The oral administration to groups or flocks of animals may have promoted the development of resistance. Knowledge about the optimal use of fluoroquinolones could help to develop appropriate dosing regimens to reduce the selection for resistance, which would ensure their future use also for the benefit of animals (Prescott et al. 2000).

The consequences of emergence of (fluoro)quinolone resistance among animal pathogens depends on the severity of the infectious disease and availability of alternative substances for the indication. The availability of potential alternatives varies between different EU-countries. In some countries, (fluoro)quinolones containing veterinary medicinal products may represent the only available treatment for certain indications in some food-producing animal species. Furthermore, for some serious indications, alternative substances may not be as efficient as (fluoro)quinolones or may already have lost their usefulness due to resistance problems. It must be emphasised that (fluoro)quinolones are valuable medicinal products also for animals, and therefore their efficacy should be retained as long as possible.

In some animal pathogens resistance to other authorised antimicrobial classes like beta-lactams, tetracyclines, trimethoprim and sulphonamides is wide spread. Consequently for some diseases antimicrobial therapy will be complicated if (fluoro)quinolones lose their activity. This is a risk for animal welfare and will result in economical losses. The best-documented example of this is *E. coli* septicaemia in poultry, because of the limited number of antimicrobials available for treatment of this animal species and the common presence of multidrug resistance (Bass et al. 1999 and Blanco et al. 1997). Other infections in which fluoroquinolones are considered important for effective treatment are pneumonia in young cattle and sheep, serious mastitis caused by Gram-negative organisms and *E. coli* neonatal diarrhoea in piglets and calves (Prescott et al. 2000).

CONCLUSIONS

1. The use of (fluoro)quinolones in animals has selected for resistance in animal pathogens and food borne zoonotic pathogens resulting in potentially negative effects on treatment of infections with these organisms in animals and humans.
2. In humans, fluoroquinolones are considered critically important antimicrobials for severe and invasive infections. These infections are predominantly caused by organisms unrelated to animals. Most of the problems with resistance in human medicine are correlated to use of antimicrobials in humans.
3. In humans treatment of uncomplicated acute gastroenteritis caused by *Salmonella* or *Campylobacter* with antibiotics is not indicated and in some countries even contra-indicated. For treatment of complicated *Salmonella* infections in humans and in patients at risk fluoroquinolones are important. Resistance to (fluoro)quinolones affects the therapeutic options, but alternative antibiotics exist. For treatment of complicated *Campylobacter* infections in humans and in patients at risk, macrolides (erythromycin, azithromycin) are considered the drugs of choice.
4. It has been reported that infections in humans with nalidixic acid resistant *Salmonella* Typhimurium have resulted in increased risk of hospitalisation and mortality. Furthermore, it has been reported that infections in humans with fluoroquinolone and macrolide resistant *Campylobacter* could result in increased risk of hospitalisation and complications.
5. For animals, fluoroquinolones are also critical, efficient and valuable antimicrobials. For some serious animal indications, fluoroquinolones are the only alternative available. If (fluoro)quinolones lose their activity or are no longer available for the treatment of animal diseases, antimicrobial therapy of some diseases will be complicated and may result in animal welfare and public health concerns, and economical losses.
6. Upon recently there was no harmonised approach in the conditions for use of (fluoro)quinolones in food-producing animals through the different Member States of the EU. International bodies (e.g. WHO, OIE) and regulatory authorities have concerns on development of antimicrobial resistance in human and animal pathogens. Antimicrobial resistance should be addressed internationally as resistant bacteria can spread via global movements of animals, animal products and people.
7. When monitoring for resistance to fluoroquinolones in *Salmonella*, nalidixic acid should be used as a marker for decreased susceptibility caused by chromosomal mutations. Because of the recent awareness of emergence of plasmid mediated quinolone resistance in Enterobacteriaceae, fluoroquinolones (such as ciprofloxacin) with epidemiological cut-off values should be used (EUCAST) besides nalidixic acid in order to detect acquired resistance optimally.
8. When monitoring for resistance to fluoroquinolones in *Campylobacter* either nalidixic acid or fluoroquinolones can be used.
9. Increasing amounts of data on the use of antimicrobial agents and the occurrence of antimicrobial resistance are available, but harmonisation still needs to be improved.
10. There is a need for risk management interventions regarding the use of fluoroquinolones for humans and animals.

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ONGOING ACTIVITIES AND SUGGESTIONS FOR ACTION

The CVMP considers that there is a need to take actions in order to maintain the efficacy of fluoroquinolone containing veterinary medicinal products. Prudent use of antimicrobials, and of fluoroquinolones specially, should be strongly promoted. Since the start of the preparation of this document, a plan for action, in line with the suggestions below, has been put into action.

The following recommendations are made:

1. Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials. The need of prophylactic use¹ should always be carefully considered and preserved for specific circumstances.
 - This should be considered in the conditions for authorisation and reflected in the SPCs.
 - Prudent use guidelines in all countries should take this into account and all Member States should take measures to ensure the implementation of such guidelines.

In order to achieve a harmonised situation in SPCs of (fluoro)quinolone containing products authorised in the EU, there is a need for harmonisation of prudent use instructions in the product literature of those products. Following a Focus Group meeting of the CVMP with Interested Parties and Member States to discuss the reflection paper and its recommendations an agreement was reached to harmonise precautionary phrases, the document “*Reflection paper on the use of fluoroquinolones in food producing animals - Precautions for use in the SPC regarding prudent use guidance*” (EMEA/CVMP/416168/2006-FINAL), provides detail on the CVMP agreement. Activities are ongoing involving the EU Authorities and the pharmaceutical industry regarding the implementation.

2. The dosage regimens of fluoroquinolones should be carefully determined on the basis of their pharmacokinetic and pharmacodynamic properties to ensure optimal efficacy and reduce selection of resistance. This should be an on-going action for the development of new fluoroquinolone-containing products.

¹ From Codex Code of practice to minimize and contain antimicrobial resistance (CAC/RCP 61-2005):
Prevention/Prophylactic Use refers to use of an antimicrobial(s) in healthy animals considered to be at risk of infection or prior to the onset of clinical infectious diseases. This treatment includes:

- control of dissemination of clinically diagnosed infectious disease identified within a group of animals, and
- prevention of an infectious disease that has not yet been clinically diagnosed.

The CVMP considers that, in order to have a global approach to the problem of antimicrobial resistance, there is a need to strongly support the following suggestions to reduce antimicrobial resistance. It is recognised that those suggestions are outside the remit of the CVMP.

Suggested action	Responsible body
<ul style="list-style-type: none"> • Veterinarians should be continuously educated on strategies to minimise antimicrobial resistance 	Universities, Veterinary Associations, national authorities (e.g. granting veterinary authorisation)
<ul style="list-style-type: none"> • Emergence of (fluoro)quinolone resistance in pathogenic and indicator bacteria should be monitored and the need for interventions should be continuously evaluated. 	The European Commission, EFSA, ECDC, Community Reference Laboratory, National Reference Laboratories and routine laboratories
<ul style="list-style-type: none"> • Use of (fluoro)quinolones should be monitored in each country and this should be done by animal species to measure the effect of interventions described above. 	Member State regulatory authorities
<ul style="list-style-type: none"> • All Member States should implement and enforce internationally recognised code of practice of rational and prudent use of antimicrobials (Codex code of practice to minimize and contain antimicrobial resistance CAC/RCP 61-2005; the OIE terrestrial code – chapter on antimicrobial resistance) 	Member States