

USE OF QUINOLONES IN FOOD ANIMALS AND POTENTIAL IMPACT ON HUMAN HEALTH

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I. Introduction

A variety of antimicrobial types are used in livestock production. Their use inevitably leads to the selection of resistant forms of bacteria in the ecosystem of use. This selection will occur with all uses in livestock production including treatment, prophylaxis and growth promotion.

Priority medical problems arising from the use of antimicrobials in livestock production have been summarized¹ recently. Use of quinolones² in livestock has been identified as a particular area of concern because of the significance of this group of antimicrobials for the treatment of a broad range of infections in humans including gastrointestinal infections caused by zoonotic bacteria transmitted to humans via the food chain.

Currently, several quinolones are available for treatment of animals, poultry and fish in many countries in the world. Available data indicate that they are also used for disease prevention in some regions. Quinolone production and usage is estimated³ to be about 50 tonnes for proprietary products (mainly USA, European Union, Japan, South Korea) and, because of their lower prices, about 70 tonnes for generic quinolones. However, available usage data, particularly for non-proprietary quinolones, are known to be grossly incomplete. For instance, data from China estimate annual quinolone consumption in animals in China alone to be in the range of 470 tonnes (annual consumption in human medicine in China: about 1,350 tonnes).

Considerable variation in the usage and in the regulatory processes for drugs of different countries is recognized to occur. Licensing requirements range from highly controlled to minimal scrutiny and in some cases the products are available without a review process by a regulatory authority. In some countries there is no legal framework for prescription of veterinary pharmaceuticals.

An increase in antimicrobial resistance in zoonotic bacteria isolated from animals, food and humans (e.g., *Salmonella* and *Campylobacter*) has already been reported, but the scope of the problems still needs to be identified and the links between quinolone use in animals and the occurrence of problems in infectious disease treatment in humans elucidated.

Against this backdrop, WHO organised a consultation to address some of the above mentioned concerns in June 1998. The objectives of this meeting were to:

- Identify known and potential links between the emergence and spread of quinolone resistance from food-borne and other possible zoonotic bacteria, and human zoonotic infection.
- Review the conditions and extent of use of the various quinolones in humans and in food animals.
- Identify and make specific recommendations on areas of applied research or data gathering that would assist in risk assessment.

The meeting gathered 59 experts from a wide range of disciplines including clinical medicine, infectious disease epidemiology and control, microbiology, veterinary medicine, animal production, licensing and registration of antimicrobials, research and development and sale of antimicrobials. In addition, representatives from numerous governmental and non-governmental organizations and observers attended the consultation.

Thirty-two presentations were delivered by participants of this meeting. Of these papers, 30 were distributed to an e-mail discussion group for comments over a 4-week period prior to the meeting in Geneva. The group included over 450 subscribers from at least 44 countries on all continents. Comments from the group were supplied to meeting participants along with the working papers, at the beginning of the meeting.

Presentations and discussions on the first two days of the meeting reviewed:

- use of quinolones and resistance in humans
- production, licensing and use of quinolones for food animals
- links between quinolone resistance in food animal bacteria and human disease.

One paper provided an overview on the possibilities and conditions of risk assessment in the context of containment of antimicrobial resistance.

Subsequently, two working groups drafted reports which were discussed and adopted during the final plenary session:

- Links between quinolone use in food animals and observed increases in quinolone-resistant food-borne pathogens and human treatment problems
- Quinolone use in animals and resistance in animal bacteria.

This report presents the findings, conclusions and recommendations of this meeting.

II. Use of quinolones in humans and emerging resistance problems

Since the development of newer quinolones and their release in the mid-1980s, there has been extensive clinical use of these agents in human medicine, and four new agents have been released in the past two years. Various quinolones have been approved and used extensively for treatment of a broad range of clinical infections, including those of the genitourinary, gastrointestinal, and respiratory tracts as well as infections of bone, joints, and skin. In the context of increasing resistance of gram-negative bacteria to other classes of antimicrobials, these agents have provided valuable alternative therapies and often been used in place of more toxic aminoglycosides. The most recently released members of the class, which have increased potency against gram-positive and in some cases anaerobic bacteria have also expanded the range of applications particularly to include intra-abdominal infections caused by mixtures of anaerobic and gram-negative bacteria and infections caused by *Streptococcus pneumoniae*, which has become increasingly resistant to other antimicrobials normally used for treatment of these infections.

With the use of quinolones in human medicine in the past decade, there has also been recognition that this use may select for resistance in human pathogens. Although many pathogens have remained susceptible (e.g., community strains of Enterobacteriaceae) with little increasing resistance in the past decade in many developed countries, there are several circumstances in which resistance has limited therapeutic use. Resistance was first recognized and has had the largest effect in *Staphylococcus aureus*, especially methicillin-resistant strains, and *Pseudomonas aeruginosa*, an occurrence which may in part reflect two factors. One factor is the finding that single mutations occurring on the chromosome of members of these species may be sufficient to cause clinically relevant levels of resistance, and the second factor is that infections with these organisms often occur in hospital settings in which nosocomial spread may occur and amplify the prevalence of resistance. Resistance, however, has also occurred in pathogens whose susceptibility is sufficient to require more than a single chromosomal mutation to develop levels of clinical resistance. One particularly important example is resistance in *Escherichia coli* isolated from blood cultures from neutropenic patients given quinolones for prophylaxis in several medical centers. Epidemiologic and microbiologic studies of these patients have clearly identified quinolone use as the principal risk factor, the occurrence of selection in distinct strains that are part of endogenous fecal flora (rather than nosocomial spread), and the presence of multiple mutations contributing to resistance. These data imply that even for highly susceptible organisms, in settings of intense selection pressure, highly resistant isolates may emerge when there is a large reservoir of organisms such as in the gastrointestinal tract that allows persistence of first-step resistant mutants from which second and later step mutants may be selected. Resistance emerging in urinary isolates of *E. coli* in Europe and resistance in *Neisseria gonorrhoeae* have also been associated with human fluoroquinolone use. There is concern that expanded use of quinolones for treatment of respiratory tract infections may pose a risk for development of resistance in *S. pneumoniae*, but data are currently limited.

For zoonotic infections, fluoroquinolones have often been used for treatment of human infections with *Campylobacter jejuni* and species of non-typhoidal *Salmonella*. For empiric treatment of bacterial gastroenteritis, which is most often caused by *C. jejuni*, *Salmonella*, *Shigella*, or *E. coli*, the fluoroquinolones are one of the few classes of agents with activity against the full range of pathogens, and thus are commonly used. Patients with bacteraemic *Salmonella* infection have also been treated with quinolones. Resistance has been documented to emerge during therapy in small numbers of cases of *Campylobacter* and *Salmonella* with a few clinical failures, but the magnitude of this problem is uncertain. In treatment of enteric fever due to *Salmonella typhi*, a non-zoonotic member of the genus, it has recently been documented that reduced susceptibility to fluoroquinolones without complete resistance (as defined by established breakpoints used in clinical laboratories) is associated with slower rates of response to quinolone therapy, raising concerns that reduced susceptibility without complete resistance in other species of *Salmonella* may affect the outcomes of quinolone therapy.

III. Links between quinolone use in food animals, observed increases in quinolone-resistant food-borne pathogens and human treatment problems

General statements

Quinolones are synthetic antibiotics that act by inhibiting DNA gyrase and topoisomerase IV in susceptible bacteria. The original quinolones have modest activity against Enterobacteriaceae and some other facultative gram-negative bacteria only. Fluorinated quinolones, called fluoroquinolones, were developed from the original quinolones and extended the spectrum of activity to include *Pseudomonas aeruginosa* and some gram-positive bacteria, as well as having substantially increased activity against other gram-negative bacteria.

Bacteria resistant to the original class of quinolones (e.g., nalidixic acid, oxolinic acid) may have reduced susceptibility or resistance to fluoroquinolones. Bacteria resistant to one fluoroquinolone are generally cross-resistant to other fluoroquinolones. This cross resistance includes fluoroquinolones used in animals and those available for human use.

Exposure to lower concentrations of quinolones increases the chance for selection of resistance. This circumstance could be encountered in certain dosing situations, with poor compliance or with poor quality products where inadequate doses could be taken by some individuals. There is controversy about the relative risks of inadequate dosing in an animal population by different routes of administration, particularly the relative risks of dosing via water and feed in comparison to other routes.

Evidence in relation to *Campylobacter*

Nature of resistance

C. jejuni and *C. coli* are naturally less susceptible to fluoroquinolones than many other gram-negative bacteria. In these species, single mutations can lead to resistance that exceeds commonly accepted breakpoints. In addition to quinolone resistance, co-resistance with other antibiotics such as macrolides has been noted in Spain and Thailand.

Campylobacter in food animals

C. jejuni is a frequent commensal in poultry and cattle, and *C. coli* is a frequent commensal in swine and poultry. There is a temporal association between the introduction of fluoroquinolones for use in poultry and a substantial rise in the prevalence of quinolone-resistant *C. jejuni* isolated in live poultry, poultry meat and from infected humans. Moreover, prior to any use in poultry, no resistant strains were reported in individuals with no previous exposure to quinolones.

Impact on human health

Campylobacter species are the commonest cause of bacterial gastroenteritis in developed countries. Sporadic cases of campylobacteriosis, which comprise the largest number of reported cases, are predominantly associated with consumption of contaminated food, particularly poultry, in most developed countries.

The majority of gastrointestinal *Campylobacter* infections do not require antibiotic treatment and are self-limiting. Where treatment is felt to be required, erythromycin is usually recommended. However, fluoroquinolones are often used for empiric treatment because they will cover other bacterial pathogens pending laboratory results. They also are better tolerated than erythromycin.

In studies in several countries, there is an association with overseas travel to areas of high prevalence of fluoroquinolone-resistant campylobacter and acquisition of such strains. However, the majority of fluoroquinolone-resistant campylobacter are domestically acquired. In the past, some studies using molecular markers have shown a link between human and animal isolates of susceptible campylobacter. Recently one US study has confirmed similar links for fluoroquinolone-resistant strains.

The effect of fluoroquinolone resistance in campylobacter on the clinical outcome of treatment with a fluoroquinolone is not clear. In immunocompromised patients there have been reports of failures associated with resistance emerging during treatment. However, there are few published data on immunocompetent individuals. There are conflicting data on whether resistant campylobacter have caused more severe disease.

Evidence in relation to non-typhoidal Salmonella

Nature of resistance

Salmonellae are normally highly susceptible to fluoroquinolones. They require two or more mutations to become resistant at levels above the most widely used clinical breakpoints (e.g., ciprofloxacin 1-4 mg/L).

Salmonella in food animals

Salmonellae have a wide host range that includes humans and animals, both as a coloniser and a cause of disease. There is a temporal association between the introduction of fluoroquinolones in food-producing animals and the emergence of reduced susceptibility to ciprofloxacin in *S. typhimurium* DT104, already resistant to five antibiotics, in the UK. There are also indications of reduced susceptibility to ciprofloxacin in human isolates of a variety of zoonotic salmonellae following introduction into food-producing animals of fluoroquinolones in the UK, USA and Denmark.

Subsequent to the introduction in 1988 of fluoroquinolones for food animal use in Germany, the emergence of fluoroquinolone-resistant variants of the multi-resistant *S. typhimurium* clone DT204c was observed. Resistance reached a prevalence of 50% in isolates from calves in a defined area of the country. Subsequently the prevalence of these resistant strains has diminished, but data associating this change in prevalence with changes in fluoroquinolone usage in animals are unavailable.

There is uncertainty about the relative contribution of direct selective pressure versus the spread of resistant strains in the presence or absence of quinolone use to the emergence and dissemination of quinolone-resistant *Salmonella*.

Variation is reported in the rate of emergence of animal strains with reduced susceptibility to fluoroquinolones in different countries after the introduction of fluoroquinolones for use in food animals. Lack of data on usage of quinolones in many countries makes interpretation of this variation difficult.

Impact on human health

Person-to-person spread of salmonellas may be common in developing countries but is rare in developed countries, where most infections are food-borne. Fluoroquinolones are important drugs for the treatment of extra-intestinal infections caused by *Salmonella*.

Prior use of antibiotics in humans increases the likelihood of contracting salmonellosis caused by susceptible but especially resistant strains.

The common serotypes of *Salmonella* cause bacteraemia in 0.5 - 2.5% of culture-confirmed salmonellosis cases in the UK and in less than 6% in the USA. Untreated or ineffectively treated salmonella bacteraemia in humans can be fatal. There has been only one published case of a non-fatal infection by *S. typhimurium* DT204c infection due to a resistant strain of animal origin that failed fluoroquinolone therapy. There is concern, however, that zoonotic salmonellae with decreased susceptibility to fluoroquinolones are increasing and that a small proportion of these will cause invasive infections that require treatment, possibly with a fluoroquinolone, and that treatment failure could occur. The emergence of extended-spectrum beta-lactamase-producing salmonellae in some locales also increases this concern because of limited treatment options.

Although there is no microbiologically proven link between antibiotic resistance and virulence for humans in zoonotic salmonella, increased rates of hospitalisation have been reported for patients with infections with multiresistant *S. typhimurium* DT104.

Prolonged carriage of fluoroquinolone-resistant salmonella has implications for food handlers and health care workers, such as delay in return to work.

Conclusions on links between quinolone use in food animals and observed increases in quinolone-resistant foodborne pathogens and human treatment problems:

The use of fluoroquinolones in food animals has led to the emergence of fluoroquinolone-resistant *Campylobacter* and of *Salmonella* with reduced susceptibility to fluoroquinolones.

There has been little documented impact of this resistance on human health to date, but there is concern about the potential human health consequences if resistance were to increase and spread. Further research and data gathering are essential to quantify this potential.

IV. Quinolone use in animals and resistance in animal bacteria

Quinolone use in animals

Nalidixic acid was developed in the early 1960's and was the first quinolone used clinically in animals. Subsequent quinolones, all congeners of nalidixic acid and synthesised in the late 1960s and 1970s, clearly showed both improved antibacterial and pharmacokinetic properties as well as reduced side effects. Some of these are still used in veterinary medicine (flumequine, oxolinic acid) in a limited number of countries. Clinically, a significant breakthrough was achieved by the introduction of the fluoroquinolones. Currently, several fluoroquinolones are available for therapy of animals in many countries. However, the usage of these fluoroquinolones differs greatly as regards animal species, indications, label indications, and geographic spread, which are summarized in Table 1 and Table 2.

The data presented indicate that quinolones are used for treatment of animal disease in many countries of the world and in some regions they are also used for disease prevention. Table 1 is not able to show that in some regions of the world there are significant amounts of generic and/or counterfeit drugs used, sometimes of unknown or variable product quality. The exact amount of this use is difficult to quantify as the usage data are not available, but it is believed to exceed the use of veterinary proprietary product(s) worldwide.

Table 1 Proprietary quinolones currently licensed for use in animals

Generic name	Trade name	cattle	swine	chickens	turkeys	Dogs	cats	fish
enrofloxacin	Baytril	X	X	X	X	X	X	X ^a
danofloxacin	Advocin, Advocid	X	X	X				
norfloxacin	Quinabic			X	X			
ofloxacin	Oxaldin			X	X			
ciprofloxacin	generic		X	X				
sarafloxacin	Floxasol Saraflox Sarafin			X	X			X
orbifloxacin	Victas Orbax	X	X			X	X	
marbofloxacin	Marbocyl	X	X			X	X	
flumequine	many	X	X	X				X
oxolinic acid	many	X	X	X				X
difloxacin	Vetequinon Dicural		X	X	X	X		

^a Baytril is not licensed for this use but generic products are available in some countries

Furthermore, limited usage data from developed countries have been available to regulatory authorities in the form of quantity (by weight) used in some countries. More specific information on the distribution of use by region, animal species and type, indication and formulation has traditionally not been available because pharmaceutical companies have tended to view these data as proprietary information. Efforts are being made in some regions to at least partially overcome this problem by third party collection and tabulation of usage data in a manner that protects confidentiality. This data collection may not, however, address the use of generic quinolones.

Although the major sources of food-borne salmonella and campylobacter are livestock and poultry, it is recognized that companion and feral animals exposed to quinolone selective pressure represent a potential source of anti-microbial resistant zoonotic bacteria for food animals, and pets are a potential source of infection for humans through direct contact. The first isolations for *Salmonella typhimurium* DT104 in the UK were from non-domestic birds and human beings. Increasingly, this zoonotic pathogen has been

Table 2 Quinolones licensed for use in food animals by region of the world

Region	Livestock	Poultry	Pet animals	Fish
Europe	enrofloxacin, flumequine, marbofloxacin, danofloxacin	enrofloxacin, difloxacin, flumequine, oxolinic acid	enrofloxacin, difloxacin, marbofloxacin	sarafloxacin, (oxolinic acid) ^a
USA	none	enrofloxacin, sarafloxacin	enrofloxacin, difloxacin, orbifloxacin	none
Japan	enrofloxacin, danofloxacin, orbifloxacin, difloxacin, oxolinic acid	enrofloxacin, danofloxacin, ofloxacin, vebufloxacin, oxolinic acid	enrofloxacin, orbifloxacin	oxolinic acid
Asia	enrofloxacin, danofloxacin, ciprofloxacin	enrofloxacin, ciprofloxacin, danofloxacin, ofloxacin, flumequine, norfloxacin, oxolinic acid, (sarafloxacin)	enrofloxacin	oxolinic acid, enrofloxacin, flumequine
Latin America	enrofloxacin, ciprofloxacin, danofloxacin, norfloxacin, (flumequine)	enrofloxacin, ciprofloxacin, danofloxacin, norfloxacin, (flumequine, oxolinic acid)	enrofloxacin	oxolinic acid
Canada		enrofloxacin ^b	enrofloxacin	
Australia	none	none	enrofloxacin	none
South Africa	enrofloxacin, danofloxacin	enrofloxacin, danofloxacin, norfloxacin	enrofloxacin	

^a Substances in parentheses are in limited use.

^b Voluntarily withdrawn from the market in 1998.

isolated from faeces of farm animals and in some countries is now endemic in these species, and it has been isolated from companion and feral animals as well. Thus, companion animal data are presented in these tables with information from food animals.

Further, the potential importance of extra label use in other species, including horses, is recognized. In some countries, veterinarians have the authority to use these products in other (extra label) indications and situations; elsewhere, veterinarians are restricted to the use of these products to label indications or specifically when no other medicinal products are available for that disease in that species. Finally, there are many developing countries where these products may be used by producers without the requirement of veterinary involvement.

As indicated in Table 3, quinolones are licensed for treatment of *Salmonella* infections in some animal species. This is noteworthy because treatment of salmonellosis with antibiotics has been shown to prolong carriage of salmonella in food animals, however

Table 3 Indications of use and formulations of quinolones for treatment of infection in animals

Animal species	Licensed use	Major bacteria	Formulations
cattle	respiratory, enteric	<i>Pasteurella</i> spp., <i>Haemophilus somnus</i> , <i>Mycoplasma bovis</i>	injectable, bolus
swine	respiratory, enteric, mastitis/metritis	<i>Pasteurella</i> spp., <i>Actinobacillus pleuropneumoniae</i> , <i>Mycoplasma</i> , <i>E. coli</i>	injectable, oral solution, feed medication
broilers	respiratory, enteric	<i>E. coli</i> , <i>Mycoplasma</i> , <i>Pasteurella</i> , <i>Salmonella</i>	oral (water medication)
turkeys	respiratory, enteric	<i>E. coli</i> , <i>Mycoplasma</i> , <i>Pasteurella</i> , <i>Salmonella</i>	oral (water medication)
fish	generalised conditions (septicemia), skin/ulcers	<i>Aeromonas hydrophila</i> <i>Vibrio</i> spp.	oral (feed medication), water bath
dogs	skins/wounds, urinary tract, respiratory	<i>S. intermedicus</i> , <i>E. coli</i> , <i>Pasteurella</i>	tablets, injectable
cats	skins/wounds, urinary tract, respiratory	<i>S. intermedicus</i> , <i>E. coli</i> , <i>Pasteurella</i>	tablets, injectable

to date this has not been shown to occur with quinolone use. There are no published data regarding the incidence of treatment failures of salmonellosis in animals caused by any strain of *Salmonella* that has reduced susceptibility (distinguished from clinical resistance) to fluoroquinolones, however there have been treatment failures in calves due to clinically resistant *Salmonellae* in Germany.

Licensing and post-licensing procedures and requirements for quinolones in various parts of the world

Considerable variation in the regulatory processes of different countries is recognized to occur. Licensing requirements range from highly controlled to minimal scrutiny and in some cases the products are available without a review process by a regulatory authority. In some countries there is no legal framework for prescription of veterinary pharmaceuticals.

The Veterinary International Cooperation on Harmonisation (VICH) is an international initiative intended to harmonise the regulatory requirements for registration among the United States, the European Union and Japan. This initiative is held under the auspices of the Office International des Epizooties (OIE). The issue of antimicrobial resistance has not been posed to the VICH, although it could be.

Some regulatory bodies have in place requirements to include the evaluation of microbiological safety in terms of resistance to antimicrobials. Technical areas required to be addressed in drug licensing in the United States, the European Union and Japan include target animal efficacy and safety, human food safety regarding drug residues, and product quality. Increasingly, countries are concerned about the emergence of resistance among zoonotic pathogens. A fundamental addition to the registration process in some countries is the evaluation of resistance concerns pre-approval and the monitoring of susceptibility of zoonotic and/or target animal pathogens post-approval as a critical part of the registration process. In some jurisdictions, issues arising for a particular product have to be addressed before renewal of the marketing authorisation. Furthermore, many groups are initiating efforts to develop principles of prudent use and to educate veterinarians and end-users about the prudent or judicious use of antimicrobials.

Quinolone resistance patterns in animal pathogens and commensals

Resistance to quinolones, in the form of nalidixic acid resistance and reduced susceptibility or clinical resistance to fluoroquinolones, has been observed in target pathogens and commensals. The acquisition of resistance has been found to develop through step-wise, chromosomal mutation, and to be directed towards both the target enzymes and the efflux pump of the bacteria.

There are vast regional differences in monitoring of the resistance patterns in animal pathogens and commensals. The majority of regions have no monitoring programmes ongoing. There are also substantial differences in the types of samples that are collected for monitoring, including clinical submissions, slaughterhouse samples, and samples collected from herds/farms/hatcheries. These are in some cases collected on an ongoing basis and in other cases are compiled for a specific period of time and for a specific purpose, such as a regional or national survey. Even with the ongoing monitoring programmes that do exist, the practising veterinarian or other user is unable to obtain easily the relevant data on a regional and national basis. Government bodies, veterinarians, pharmaceutical companies and the food-producing industry may be conducting independent monitoring programmes, but efforts and procedures differ, resulting in data from different laboratories and countries that in some (perhaps most) cases cannot be compared. This same dilemma exists when attempting to compare data from different regions.

In addition to monitoring programmes as a source of resistance data, in many countries there are private or public animal disease diagnostic laboratories that conduct bacterial culture and antimicrobial susceptibility analyses on clinical submissions. Veterinarians use this information to evaluate the need for quinolone treatment of animals. Furthermore, regulatory agencies may use some of these data or specimens (especially of zoonotic agents) to assess the emergence and transmission of resistance in zoonotic food-borne bacteria.

V. Recommendations

Research needs

Applied research should be conducted:

- to further evaluate the impact of bacteria with reduced susceptibility to fluoroquinolones on the outcome of treatment of human infections
- on established and novel mechanisms of resistance to quinolones in food-borne pathogens
- on emergence and dissemination of quinolone resistance in zoonotic bacteria and its spread within and between species. Specific research subjects would be the spread of fluoroquinolone-resistant bacteria from animals to farm workers and the establishment of the clonal relationships between quinolone-resistant strains in animals and humans
- on the persistence of quinolone-resistant strains compared to susceptible strains of *Campylobacter* and *Salmonella*, particularly in food animals
- on methods and tools that would reduce the risk of selecting bacteria with quinolone resistance or reduced susceptibility in animals and that would lead to the restoration of susceptible flora after resistance. This would include research into:
 - the appropriate dose, route and duration of administration of quinolones in animals. In particular, studies are needed on the relative risks of dosing via water and feed in comparison to other routes
 - a broad range of animal production and management practices.

Similar studies to evaluate the effects of reduction of use of quinolones on restoration of susceptible flora are also needed.

- to develop economical alternatives to the use of antimicrobials for disease prevention (e.g., vaccines, probiotics, competitive exclusion principles, etc.) and evaluate the impact that these alternatives might have on selection for resistance
- to evaluate the impact of the use of quinolones in domestic pets and birds on the introduction, development, and persistence of resistant bacteria in the farm environment
- on the epidemiology of food-borne pathogens.

In addition, there is a critical need to investigate methods and procedures to appropriately address resistance concerns that arise prior to licensing of quinolones. This research should define the appropriate risk assessment models and data needed to allow the models to be implemented. Additionally, the most appropriate post-approval monitoring schemes should be developed which complement the pre-approval risk assessment models.

Data gathering needs

Gathering of surveillance data on resistance levels and drug usage is critically important for assessments of risk. Specifically, there are five purposes to monitoring occurrence of resistance in zoonotic pathogens, and these are to:

- assist in clinical decisions
- provide information for the development of new drugs
- target and evaluate prevention and control measures (including prudent antimicrobial use) and epidemiology
- identify trends in antibiotic resistance patterns
- inform public policy with information for risk assessment and antimicrobial use.

Quinolone usage data should be accessible to the regulatory authorities to help interpret the related resistance surveillance data.

Monitoring of antimicrobial resistance

- In order to generate more reliable and comparable data, it is recommended that there be international co-ordination on surveillance methods and data exchange.
- The recommendations for surveillance methodologies as outlined in the Berlin document (proper reference) are re-emphasized.
- Resistance monitoring should be targeted to include at least *E. coli*, Salmonella, and Campylobacter isolated from animals.
- Laboratory susceptibility testing techniques, including breakpoints used in public health and food chain monitoring, should be standardised with a view to provide comparable data.
- Surveillance should ideally be structured to allow elements of both local monitoring and reporting as surveillance systems often pool data regionally or nationally. Thus, problems occurring at the level of the individual farm that are important for control of local resistance can be masked.
- Research should be undertaken to determine the optimum surveillance sampling schemes required to fulfil the objectives of the monitoring programme (i.e., to detect resistance emergence vs. to monitor the safety of the food supply).
- Components for monitoring of resistance
 - national quality control
 - international standardisation and co-ordination of methods of susceptibility testing.
- For resistance to fluoroquinolones, quantitative susceptibility data and categorical nalidixic acid resistance data are more sensitive for the detection of common first-step mutations that cause reduced susceptibility than are categorical fluoroquinolone resistance data.

Usage of quinolones in food animals

There is a need to acquire more and better information on quinolone usage in food animals. Information should also include generic drug use. Documentation of total usage at the national level by species, product class, indications, dose and geographical region is a first step. Availability of these data is critical for more accurate risk assessment. Ideally these data should be linked to epidemiological investigations. The more specific the consumption data, the better the ability to interpret any changes in resistance. If necessary, governments could either handle these data in a confidential and proprietary manner from the drug sponsor, or could survey end-users regarding prescribing practices or even require submission of consumption and usage data.

Prudent use of antimicrobials in livestock

As an element to further encourage activities for the prudent use of antimicrobials in livestock WHO should take leadership with the Food and Agriculture Organization (FAO) and the OIE to convene, in collaboration with other international and intergovernmental organisations, an expert consultation to develop a code of practice for prudent use of antimicrobials in food animal production. WHO should ensure that public health safeguards are considered in the development of the code of practice.

The following proposals of the participants of this meeting should be considered at such a consultation:

- Veterinarians should have at their disposal antibiotics to treat sick animals, which in certain instances may include quinolones. Quinolones, as with any antimicrobial agent, should never be used as a substitute for good animal husbandry practices. Quinolones should be administered in accordance with prudent use principles. Prudent use of quinolones is defined as the practices that maximize therapeutic effect while minimising the emergence of resistance.
- Member States should be encouraged to promote prudent use of quinolones in veterinary medicine. Specifically for quinolones, prudent use includes, but is not limited to:
 - (a) treatment only under close supervision of a veterinarian for animals under his/her care with written records of use
 - (b) treatment upon a diagnosis based, whenever possible, on bacterial culture and susceptibility testing with the encouragement of accurate on-farm record-keeping
 - (c) when culture and susceptibility culture results are known, an efficacious narrow-spectrum antibiotic is preferable for therapy over quinolones.

- Education of veterinarians and end-users about prudent use principles is critical to their implementation and should cover the risks of selecting resistant bacteria, the fundamental understanding of antimicrobials and prudent use concepts. Veterinary educators should be encouraged to ensure that these prudent use principles are included in veterinary curricula.
- Registration of quinolones should be only for therapeutic use and not for performance enhancement. They should be registered only as prescription veterinary pharmaceuticals, with appropriate enforcement of that requirement.
- No quinolones should be administered to a food animal unless the product has been evaluated and authorised by competent authorities, including a thorough assessment which considers the potential for development of resistance that may affect public health, and encouraging a post-approval monitoring programme to detect trends toward the emergence of resistance of public health significance. Authorities should be encouraged to utilize the data collected through such a monitoring programme to take measures to mitigate the development of resistance.
- Use of quinolones in food animals other than the licensed indications for use should be discouraged.

Aquaculture

Quinolone use in aquaculture was not discussed at this consultation. Because of the unique use of quinolones in aquaculture, investigation of the public health impact of this use is critical and should be facilitated by WHO.

Notes

1. *The Medical Impact of the Use of Antimicrobials in Food Animals, Report of a WHO Meeting, Berlin, Germany, 13-17 October 1997; WHO/EMC/ZOO/97.4.*
2. *This term is used in reference to all generations of quinolones, including fluoroquinolones.*
3. *Information from working paper number 9, "Overview of quinolone usage for food-producing animals" submitted by van Diest and de Jong.*

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