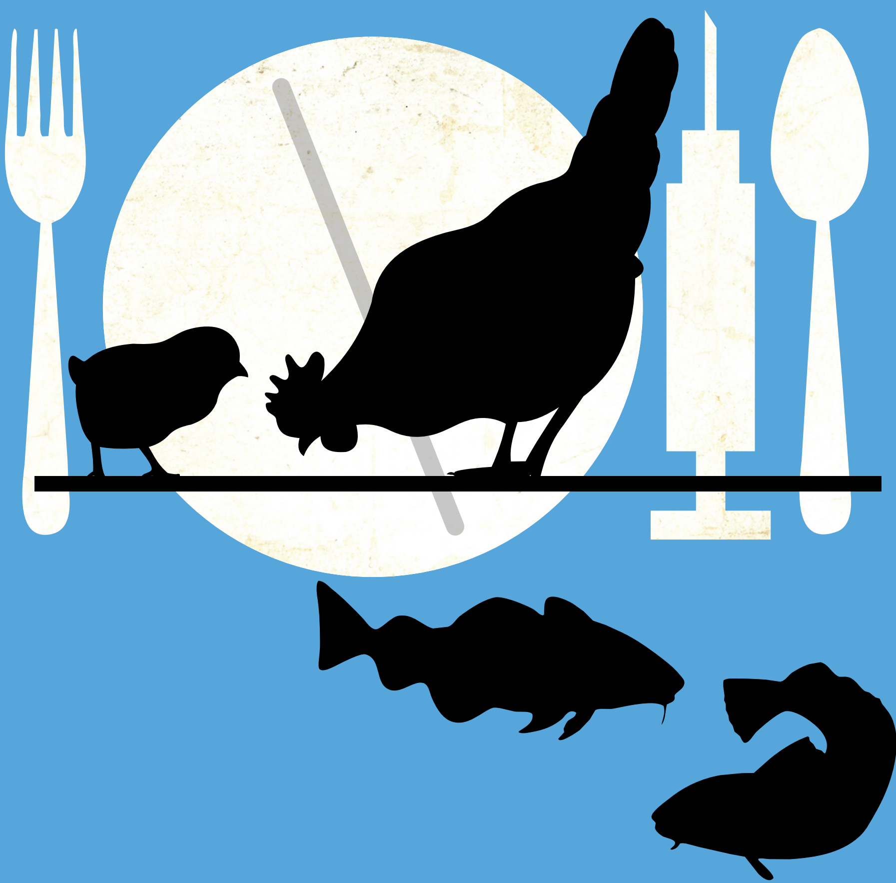
World Health Organization
REGIONAL OFFICE FOR Europe

Tackling antibiotic resistance from a food safety perspective in Europe



Antibiotics have revolutionized the treatment of infectious diseases. But their use and misuse have resulted in the development and spread of antibiotic resistance. This is now a significant health problem: each year in the European Union alone, over 25 000 people die from infections caused by antibiotic-resistant bacteria. Antibiotic resistance is also a food safety problem: antibiotic use in food animals –for treatment, disease prevention or growth promotion – allows resistant bacteria and resistance genes to spread from food animals to humans through the food-chain.

This publication explores the options for prevention and containment of antibiotic resistance in the food-chain through national coordination and international cooperation, including the regulation and reduction of antibiotic use in food animals, training and capacity building, surveillance of resistance trends and antibiotic usage, promotion of knowledge and research, and advocacy and communication to raise awareness of the issues.

This publication is primarily intended for policy-makers and authorities working in the public health, agriculture, food production and veterinary sectors, and offers them ways to take a holistic, intersectoral, multifaceted approach to this growing problem.

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Tackling antibiotic resistance from a food safety perspective in Europe

The World Health Organization was established in 1948 as the specialized agency of the United Nations serving as the directing and coordinating authority for international health matters and public health. One of WHO's constitutional functions is to provide objective and reliable information and advice in the field of human health. It fulfils this responsibility in part through its publications programmes, seeking to help countries make policies that benefit public health and address their most pressing public health concerns.

The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health problems of the countries it serves. The European Region embraces some 880 million people living in an area stretching from the Arctic Ocean in the north and the Mediterranean Sea in the south and from the Atlantic Ocean in the west to the Pacific Ocean in the east. The European programme of WHO supports all countries in the Region in developing and sustaining their own health policies, systems and programmes; preventing and overcoming threats to health; preparing for future health challenges; and advocating and implementing public health activities.

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1 The views expressed in this publication (conclusions and action points) do not necessarily reflect the views of OIE.

2 The views expressed in this publication are those of the contributors and do not necessarily reflect the views of FAO.

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Acronyms

AGP	antibiotic growth promoter
DTs	definitive phage types
ECDC	European Centre for Disease Prevention and Control
EFSA	European Food Safety Authority
EMA	European Medicines Agency
ESBLs	extended-spectrum β-lactamases
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
MRLs	maximum residue limits
OIE	World Organisation for Animal Health
TESSy	the European Surveillance System
WTO	World Trade Organization

Foreword

Infections caused by antibiotic-resistant bacteria are increasing in the community and in health care settings, becoming a major public health problem that challenges the health care systems in countries in the WHO European Region. Owing to the use and misuse of antibiotics, resistance can develop in bacteria in human beings and animals, and infections that normally respond to antibiotic treatment can become difficult and sometimes impossible to cure. The resulting treatment failures lead to increased disease cases and deaths, a growing challenge to develop new antibiotics and consequently higher costs to society. For example, more than 25 000 people in the European Union die from infections caused by antibiotic-resistant bacteria each year.

To ensure effectiveness of treatment, action is urgently needed to counteract the further development and spread of antibiotic resistance, which is driven by antibiotic use in all sectors. Since this resistance has no ecological, sectoral or geographical borders, its appearance in one sector or country affects resistance in other sectors and countries. National authorities, veterinarians, physicians, patients and farmers all have key roles in preserving the power of antibiotics. The prevention and containment of antibiotic resistance therefore requires addressing all risk factors for the development and spread of antibiotic resistance across the full spectrum of conditions, sectors, settings (from health care to use in food-animal production) and countries.

Following resolutions by the World Health Assembly (its governing body), WHO supports Member States' efforts to prevent and contain antibiotic resistance, encouraging a holistic, multifaceted, intersectoral and collaborative approach. To raise awareness about the importance of addressing this growing threat to public health, WHO has made antibiotic resistance the theme of World Health Day 2011.

In the European Region, the WHO Regional Office for Europe is developing a regional strategy on antibiotic resistance for submission to the WHO Regional Committee for Europe in September 2011. In particular, WHO has long recognized that antibiotic use in food animals, which seems to outweigh antibiotic use for human therapy in many countries, contributes importantly to the public health problem of antibiotic resistance. This necessitates increased awareness and specific policy guidance on containing antibiotic resistance from a food safety perspective.

The WHO Regional Office for Europe developed this publication, the first of its kind, to meet Member States' needs and support their efforts to prevent and contain antibiotic resistance, by focusing on spread though the food-chain, which *plays an important although often hidden role. The booklet is primarily intended for policy-makers and authorities working in the public health, agriculture, food production and veterinary sectors. It aims to raise awareness of the importance of antibiotic resistance as a food safety issue and the responsibilities of all players in food production to prevent and control the spread of antibiotic resistance through the food-chain. We at WHO hope that this booklet, offering options for prevention and containment, will support countries in developing and carrying out policies to contain antibiotic resistance and protect human health.*

Zsuzsanna Jakab
WHO Regional Director for Europe

Executive summary

A global threat

In the 1940s, the introduction of antibiotics to treat infectious diseases revolutionized medicine. Unfortunately, the use and misuse of antibiotics have also resulted in the development and spread of antibiotic resistance, which causes treatment failures and consequently more severe and longer-lasting diseases, increased hospitalization rates, more deaths, and higher costs to society. Antibiotic resistance has become a growing international public health problem that urgently requires significant attention. The magnitude of the problem is illustrated by the fact that more than 25 000 people in the European Union die each year from infections caused by antibiotic-resistant bacteria. Any kind of antibiotic use in people, animals or plants can promote the development and spread of antibiotic resistance. Also, antibiotic resistance does not respect geographical or biological borders. Thus, the use of antibiotics in one sector, setting or country affects the spread of resistance in others.

An important food safety problem

Antibiotics are used not only to treat food animals but also to prevent them from developing diseases and to promote their growth. In many countries, use in animals seems to outweigh that in human beings. Abuse in food animals has important consequences for public health, as it promotes the development of antibiotic-resistant bacteria and resistance genes that can be passed on to people. This usually occurs through the consumption of food, but also through direct contact with food animals or environmental mechanisms. Ultimately, this can result in human infections with antibiotic-resistant bacteria that can be difficult or impossible to cure. Also, because food animals and foods of animal origin are traded worldwide, they contribute to antibiotic resistance in countries far from those where the problem originates.

Resistance in the foodborne zoonotic bacteria *Salmonella* and *Campylobacter* is clearly linked to antibiotic use in food animals, and foodborne diseases caused by such resistant bacteria are well documented in people. Of special concern is resistance to so-called critically important antibiotics for human medicine. For example, the use of fluoroquinolones in food animals has led to a corresponding antibiotic resistance in *Salmonella* and *Campylobacter* species, thus causing infections in people. Also, antibiotic resistance in *Salmonella* has been associated with more frequent and longer hospitalization, longer illness, a higher risk of invasive infection and a twofold increase in the risk of death in the two years after infection. Treatment failures, increased hospitalization and a higher risk of death have been reported for multiresistant *Salmonella* Typhimurium definitive phage type (DT)104 that exhibits quinolone resistance. Moreover, compared with infections susceptible to antibiotics, infections with macrolide-resistant *Campylobacter* in people are associated with more frequent invasive illness and death.

Because the use of antibiotics as growth promoters has been shown to cause risks to human health, all antibiotic growth promoters have been withdrawn in the European Union since 2006. Discontinuing the use of antibiotic growth promoters would reduce the risk to human health without harming animal health or the economics of animal production.

In aquaculture, improved management of fish farms and the introduction of effective vaccines can significantly reduce the usage of antibiotics. This illustrates a key lesson about the importance of disease prevention that is relevant to all food-animal production.

Urgent need for action

The need to act now is clear. Tackling antibiotic resistance requires a holistic, intersectoral and multifaceted approach with effective coordination of action and exchange of information among the agricultural, food, veterinary and health sectors. Efforts should focus on reducing the unnecessary use of antibiotics and reducing the spread of antibiotic-resistant bacteria. While international cross-sectoral collaboration is essential, countries' taking a national approach to antibiotic resistance and food safety is of the utmost importance.

Overall coordination

To tackle antibiotic resistance, a national government could establish an intersectoral national strategy and action plan on antibiotic resistance. This approach, supported by an intergovernmental steering committee, would include food safety and should promote the prudent use of antibiotics in all sectors. This calls for the establishment of a formal mechanism of interaction between the health ministry and other relevant ministries and authorities to address antibiotic resistance in the food-chain.

Regulation

Regulating the use of antibiotics in food animals is an important part of containing resistance. It is suggested that national veterinary, agricultural and pharmaceutical authorities, among others, consider:

- eliminating the use of antibiotics as growth promoters;
- requiring that antibiotics be administered to animals only when prescribed by a veterinarian; and
- requiring that antibiotics identified as critically important in human medicine – especially fluoroquinolones and third- and fourth-generation cephalosporins – only be used in food animals when their use is justified.

Reduced need for and prudent use of antibiotics in animal husbandry

Antibiotics are valuable medicines, and should be used only therapeutically and as little as necessary. It is important that national veterinary, agricultural and pharmaceutical authorities promote preventive veterinary medicine and the prudent use of antibiotics in collaboration with the private sector and all relevant stakeholders, particularly veterinary practitioners and farmers. Particularly important steps are:

- reducing the need for antibiotics in animal husbandry by improving animal health through biosecurity measures, disease prevention (including the introduction of effective vaccines), and good hygienic and management practices; and
- eliminating economic incentives that facilitate the inappropriate prescription of antibiotics.

Surveillance

To monitor trends in resistance and allow for timely corrective action and evaluation of interventions, it is suggested that public health, veterinary and food authorities consider:

- establishing a surveillance system for the usage of antibiotics in people and food animals; and
- establishing an integrated (among the public health, food and veterinary sectors) surveillance system to monitor antibiotic resistance in selected foodborne bacteria.

Advocacy and communication

Promoting advocacy and communication activities is important. Such activities can raise awareness of antibiotic resistance from a food safety perspective, and prompt action that prevents its development and spread in the food-chain.

Training and capacity building

Among other things, it is suggested that veterinary, agriculture and food authorities consider developing guidelines on the prudent use of antibiotics in food animals, taking a multidisciplinary approach. Such guidelines should cover antibiotics categorized as critically important for human medicine. The authorities should also provide the training needed to implement the guidelines.

Knowledge gaps and research needs

It is suggested that national authorities, in collaboration with the private sector, support studies that help provide comparable data on antibiotic resistance and usage for risk assessment and risk management. Support is also needed to strengthen research on the development and spread of resistance, and the development of new antibiotics and alternative approaches to antibiotic therapy.

International cooperation to support national action

Tackling antibiotic resistance as it relates to food safety requires international recognition, involvement and partnership that can guide and support national initiatives. For a long time, WHO, the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE) have recognized the importance of antibiotic resistance, including in relation to food safety. This has resulted in international commitment to deal with the problem and to develop guidance to support action. In particular, World Health Assembly resolution WHA51.17 urged Member States to encourage the reduced and rational use of antibiotics in food animals. This resulted in the further development of WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food, which were developed with the participation of FAO and OIE and included in the WHO Global Strategy for Containment of Antimicrobial Resistance. The WHO Regional Office for Europe is developing a strategy on antibiotic resistance, and addressing antibiotic resistance in the food-chain is one of the key objectives of this strategy. The Codex Alimentarius Commission (part of the Joint FAO/WHO Food Standards Programme) and OIE have developed guidelines on the prudent use of antibiotics in food animals. In addition, the European Union is giving antibiotic resistance a significant amount of attention.

Introduction – Antibiotic resistance as a global threat

Definitions

Antibiotics are the primary tools for treating bacterial infectious diseases. In the 1940s, the introduction of antibiotics revolutionized medicine: it saved the lives of millions of people with pneumonia, sepsis, meningitis, severe wound infections and urinary tract infections. Also, many modern medical practices – including organ transplantation, chemotherapy for cancer and orthopaedic surgery – would be high-risk procedures without the availability of antibiotics. Box 1 discusses the terms used for antimicrobial agents.

Box 1. Choosing terms

Antimicrobial agents (or more simply antimicrobials) are chemical compounds that kill or inhibit the growth of microorganisms. They are produced naturally by such microorganisms as fungi (for example, penicillin) and bacteria (for example, tetracycline), or can be produced synthetically or semisynthetically (for example, fluoroquinolones and amoxicillin, respectively). According to the original definition by the Nobel laureate Selman Waksman, the term *antibiotic* only refers to natural compounds of microbial origin. Nevertheless, the term is often used as a synonym for any antimicrobial agent, whether natural or synthetic. Antimicrobials that target bacteria are generally called antibacterial agents. This publication uses the term antibiotics to refer to antibacterial agents used to treat bacterial infections in both people and animals.

Regrettably, soon after the introduction of each new type of antibiotic, bacteria evolved, becoming able to withstand the effect and presence of the antibiotic that previously killed them and to multiply – that is, they became resistant. The term *antibiotic resistance* refers to situations where antibiotics that normally inhibit certain types of bacteria no longer have the desired effect. Resistance to an antibiotic typically develops from its use and is a classic example of Darwin's principle, "survival of the fittest".

The epidemiology of antibiotic resistance is made more complicated by the ability of genes responsible for such resistance to spread between different types of bacteria. Also, antibiotic-resistant bacteria can spread across sectors, settings and geographical borders. This spread can be attributed to people, animals, animal products or environmental contamination.

Some bacteria resistant to antibiotics

Source: Centers for Disease Control and Prevention

Challenge for human health

Today, antibiotic resistance has become a significant and increasing public health problem internationally. Owing to antibiotic resistance, infections that normally responded to antibiotic treatment have become difficult and sometimes impossible to cure. This causes treatment failures and increased morbidity, mortality and costs to society. Resistance in different classes of antibiotics is steadily increasing among different types of bacteria and in different ecological settings and environments. Thus, previously effective antibiotics are losing their power, and health care is approaching a situation similar to the pre-antibiotic era. The value of antibiotics as life-saving medicines is threatened *(1)*.

Growing resistance to antibiotics threatens their effectiveness. As a result, people remain seriously ill for longer periods or even die from infections with resistant organisms that cannot be treated. Each year, in the European Union (EU), about 25 000 patients die from infections caused by antibiotic-resistant bacteria *(2)*. Often, alternative antibiotic therapies for resistant infections are more toxic, less effective and more expensive, and require longer treatment. In high-income health care settings, the adverse effects on health of resistance can be mitigated to some degree through the routine application of laboratory susceptibility testing, to guide antibiotic therapy decisions, and the use of

Antibiotic resistance: a serious health risk

expensive antibiotics of last resort. In low-income communities, blind therapy with a limited number of ineffective antibiotics often leads directly to treatment failure, prolonged suffering, long-term disability and increased mortality rates. Resistance also affects animal health, as sick animals may also require treatment with antibiotics.

Other factors add to the challenges of antibiotic resistance. For example, research to develop new antibiotics is very costly and lengthy, and resistance often develops rapidly after new products are marketed.

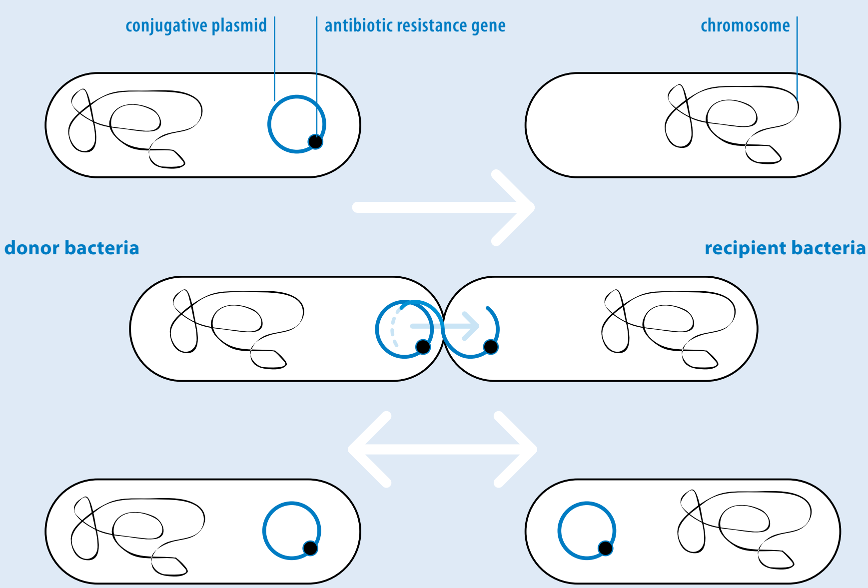
Why antibiotic resistance is increasing worldwide

The use of antibiotics for any purpose – in people, animals, plants – anywhere in the world affects everyone. Antibiotic use in one individual can promote the local survival of resistant strains that can subsequently spread from that individual to others and potentially, over time, to any community worldwide. Consequently, antibiotics have been described as *societal drugs*, in recognition of the possible global impact of individual decisions to use antibiotics.

Some bacteria have been resistant since ancient times, and are said to have natural or intrinsic resistance. In other cases, susceptible bacteria have become resistant over the course of the last several decades: acquired resistance. Bacteria are remarkably resilient and adaptable and can change rapidly in response to a change in their environment, such as the presence of an antibiotic. They are simply trying to survive.

A susceptible bacterium can become resistant through a novel genetic mutation in its DNA (chromosomal resistance) or, more commonly, through the acquisition of mobile genetic elements from another bacterium that is already resistant (horizontal gene transfer) (Fig. 1). Complicating matters is the ability of one resistance gene to often confer resistance to two or more antibiotics that usually belong to the same antibiotic class, so-called *cross-resistance*. Also, different resistant genes that confer resistance to different antibiotic classes are often located together in the DNA of the bacteria and can be transferred simultaneously (referred to as *co-resistance*). Thus, usage of one type of antibiotic can result in resistance not only to this antibiotic but also to others in the same class (*cross-selection*) or in other classes (*co-selection*).

Fig. 1. Horizontal gene transfer: resistance gene being transferred from one bacterium to another



When a bacterium becomes resistant to an antibiotic through a novel mutation in its DNA, the spread of the strain itself is the principal method of spreading the resistance. As bacteria reproduce very rapidly, organisms with this new resistance can rapidly become dominant in a bacterial population within an individual or an animal, particularly if the use of an antibiotic to which the strain is resistant wipes out competing bacteria in its immediate environment. The subsequent spread of resistant organisms through people or animals, or both, can ensure that the resistant organism becomes widely dispersed.

The consequences of horizontal gene transfer are even more alarming. This mechanism can often promote the simultaneous spread of resistance to several unrelated classes of antibiotics, particularly if the genes for such resistance are co-located on the transmissible genetic element.

Also, there is another important mechanism. When resistance has developed, bacteria may often retain it for long periods in the absence of exposure to antibiotics. This may lead to persistence of resistance to antibiotics that are either rarely or no longer used.

To make matters worse, sometimes genes for resistance and virulence can be transferred together, leading to the emergence of new resistance threats of greater virulence and pathogenicity than seen in past generations. The mass media often call such pathogens *superbugs*.

The quantitative explosion of resistance from individual cellular events (mutation and/or gene transfer) to global health challenges has relied on two additional aspects:

(a) antibiotic selection pressure
(b) demographic and geographic spread.

Since antibiotics kill susceptible bacteria, resistant bacteria have less competition for resources and can flourish, especially when antibiotics are present. Antibiotic-resistant bacteria can become established and persist, even after antibiotic use is discontinued.

People and animals normally carry vast numbers of diverse bacteria in the gut, on the skin and on other surfaces. Resistant bacteria can be carried by people and animals that are not sick, and transferred between individuals and communities, and around the world from people, animals, food and trade goods that carry them and from waterways.

Tackling antibiotic resistance

The need to act now is urgent. The ominous trend of rising antibiotic resistance is unabated, and few new antibiotics are in the pipeline. To preserve the effectiveness of antibiotics, a number of sectors must work together.

As genetic mutations and gene movements in bacteria cannot be prevented, efforts to contain antibiotic resistance must thus focus on:

- reducing unnecessary use of antibiotics and promoting their prudent use, to minimize development of resistance; and
- interrupting the spread of antibiotic-resistant strains between individuals and communities through improved infection control and measures for prevention (including vaccinations), hygiene and biosecurity.

Tackling antibiotic resistance requires international recognition, involvement and partnership that can guide and support national initiatives. With the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE), WHO has long recognized the importance of antibiotic resistance. In Europe, the EU has made the Community Strategy against antimicrobial resistance *(3)*. Annex 1 gives an overview of the activities of WHO, FAO, the Codex Alimentarius Commission, OIE and the EU.

The 1998 World Health Assembly resolution WHA51.17 *(4)* recognizes the public health importance of antibiotic resistance. It urges WHO and its Member States to take actions in surveillance, education, and policy development and implementation, including "measures to encourage the reduced use of antimicrobials in food-animal production".

WHO issued the Global Strategy for Containment of Antimicrobial Resistance in 2001 *(5)*. It covers key points required to respond to this problem, such as disease prevention, access to and appropriate use of antibiotics, surveillance, and the need for appropriate legislation and focused research. Directed to policy-makers and managers in a range of sectors and agencies, the Strategy aims to persuade governments to take urgent action and then to guide this action with expert technical and practical advice. Foremost among the recommendations was to "make the containment of antimicrobial resistance a national priority" with directives to "create a national intersectoral task force" with membership including "health care professionals, veterinarians, agriculturalists, pharmaceutical manufacturers, government, media representatives, consumers and other interested parties" *(5)*. The Global Strategy also recommends interventions to reduce the overuse and misuse of antibiotics in food animals for the protection of human health, based on the WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food *(6)*.

In 2005, the World Health Assembly adopted resolution WHA58.27 to improve the containment of antimicrobial resistance *(7)*, by:

- ensuring the development of a coherent, comprehensive and integrated national approach to implementing the strategy for containment of antibiotic resistance;
- mobilizing human and financial resources to minimize the development and spread of antibiotic resistance; and
- effectively monitoring and controlling health-care-acquired (nosocomial) infections.

The WHO Regional Office for Europe – recognizing that antibiotic resistance is an increasing public health priority that needs to be tackled with a holistic and intersectoral approach – is developing a regional strategy on antibiotic resistance, to be presented to its governing body, the Regional Committee, in September 2011. It pursues the overall goal of reducing the morbidity and mortality associated with antibiotic resistance through seven strategic objectives:

1. to strengthen national multisectoral coordination for the containment of antibiotic resistance;
2. to strengthen national surveillance of antibiotic resistance;
3. to promote national strategies for the rational use of antibiotics and strengthen national surveillance of antibiotic consumption;
4. to strengthen infection control and surveillance of antibiotic resistance in health care settings;
5. to prevent and control the development and spread of antibiotic resistance in the food-chain;
6. to promote innovation and research on new drugs and technology; and
7. to improve awareness, patient safety and partnership.

Member States will use the strategy to develop national strategies and action plans on antibiotic resistance. As the issue is complex, and involves many sectors of society (both governmental and private), the implementation of a national plan of action, coordinated by a national multisectoral committee, should be developed and anchored in different sectors of the health care system and the veterinary sector.

This booklet specifically addresses the need to prevent and control antibiotic resistance in the veterinary and agricultural sectors: one of the key action areas highlighted in the proposed regional strategy. All these areas should be addressed at the national level. This booklet is also a response to the initiatives of international and regional organizations, including WHO, FAO, the Codex Alimentarius Commission, OIE and the European Commission. During the past 15 years, they have increasingly recognized that antibiotic resistance is also a food safety issue and that efforts are needed to protect public health by controlling the use of antibiotics in food animals.

1. Antibiotic resistance in relation to food safety

Antibiotic use in food production

Why antibiotics are used

Following the dramatic breakthrough in the control of bacterial infections in people after the introduction of antibiotics in the early 1940s, these drugs were introduced in veterinary medicine in the 1950s. Antibiotics are used in animals for therapy, disease prevention (prophylaxis) and growth promotion. The same classes of antibiotics are used in animals as those used medicinally in people. Due to the large numbers of animals and the industrialized production of food animals, the quantity of antibiotics used in food production in many countries seems to exceed the amounts used medicinally in people.

Veterinarian using antibiotic in treatment

© Gettyimages

In food animals, antibiotics are predominantly used to treat respiratory and enteric infections in groups of intensively fed animals. They are used especially during the early part of an animal's life – for example, in broiler chickens and in weaning pigs and calves. Antibiotics are also used to treat infections in individual animals caused by a variety of bacterial pathogens. In particular, antibiotics are often used to treat mastitis in dairy cows, common infections in cows with a high milk output.

Further, the global increase in intensive fish farming has been accompanied by bacterial infections that are usually treated with antibiotics added to fish foodstuffs. Similar to other industrialized food-animal production, the usage of antibiotics in aquaculture can be substantial.

Moreover, in some countries, certain antibiotics, such as streptomycin, can be used to control different diseases in plants. Few data on this are available, however, and few studies address the potential implications for human health.

Antibiotic growth promoters and lessons learned

In many countries, producers add antibiotics to the feed of terrestrial food animals in subtherapeutic concentrations (doses lower than those needed to treat infections) to improve growth, thus acting as antibiotic growth promoters (AGPs). The mechanisms by which AGPs affect feed efficiency and weight gain are not fully understood.

After being introduced in the 1950s, AGPs were introduced globally for routine use in intensively raised food animals, regardless of the animals' health status or the risk of bacterial infection. This led to an explosive increase in the overall usage of antibiotics in many countries. For example, in the United States, the use of antibiotics as AGPs increased fiftyfold between 1951 and 1978 (from 110 tonnes to 5580 tonnes), while there was only a tenfold increase in the use of antibiotics to treat infections in people and animals *(8,9)*; during this period, many bacterial strains from both human and animal sources that were previously susceptible to antibiotics became resistant. Similar results were reported for several other countries. For example, in England (United Kingdom), the prevalence of tetracycline-resistant *Escherichia coli* in poultry increased from 3.5% to 63.2% after only four years (1957–1960) of the antibiotic's use in poultry *(10)*.

Initially, virtually all antibiotics could be used as AGPs, and the doses given were subtherapeutic. In Great Britain in 1968, concerns about the possible adverse effects on human health led to the appointment of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine, chaired by M.M. Swann. The subsequent report *(11)* recommended that antibiotics should not be used as AGPs if they were used as therapeutic agents in human or animal medicine or were associated with the development of cross-resistance to antibiotics used in people. The Swann report was the foundation for the development of the policy of prudent use of antibiotics and for regulations in many western European countries.

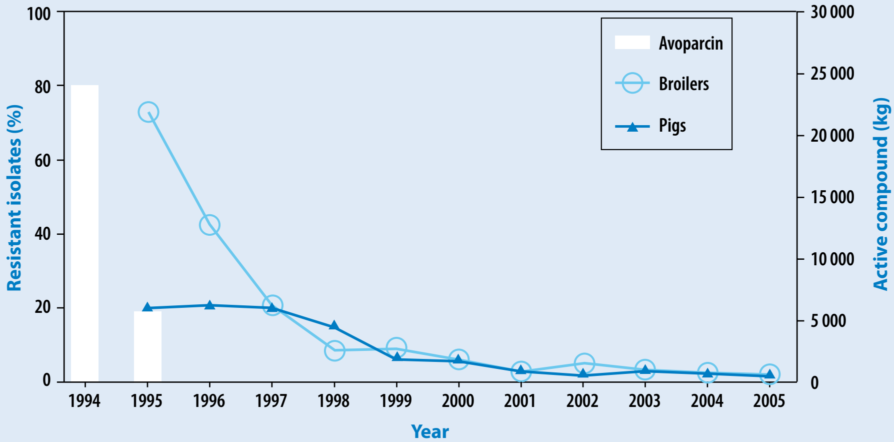
Nevertheless, the global use of AGPs continued until 1986, when Sweden banned their use. During the subsequent 10 years, concern grew about the continuous increase in antibiotic resistance. Researchers found that the use of antibiotics in food animals could pose a risk to human health, owing to the spread of resistance via the food-chain. In particular, researchers showed that AGP use represented health risks due to the development and spread of cross-resistance to antibiotics used to treat people. Some countries therefore withdrew market authorizations of individual antibiotics as AGPs: for example, Denmark and Norway banned avoparcin in 1995. Subsequently, the market authorization of avoparcin in the EU was withdrawn in 1997. The threat of antibiotic resistance also caused strong consumer reactions, as indicated by recommendations for the responsible use of antibiotics by the EU's Economic and Social Committee *(12)*.

Various countries have made risk assessments of the use of AGPs, showing that it represents a risk to human health. Since 1997, WHO has addressed the risk to public health, and recommended that the use of AGPs be stopped or rapidly phased out *(5)*. Since 2006, all AGPs have been withdrawn in the EU, following the advice of its Scientific Steering Committee *(13)*. In the European Region, apart from the EU Member States and the countries harmonizing their food safety regulations with the EU's, several countries have not yet withdrawn AGPs from the market.

The effect on the occurrence of resistance following withdrawal of AGPs in the EU has been studied, especially in Denmark. WHO convened a multidisciplinary, international expert panel to review the potential effects on human health, animal health and welfare, the environment impact, animal production and the national economy resulting from Denmark's termination of the use of AGPs in food-animal production, particularly swine and broiler chickens *(14)*. Among other things, the panel found that the animal reservoir of enterococci resistant to the AGPs used had decreased significantly. Fig. 2 shows the trends in glycopeptide resistance among *Enterococcus faecium* from broiler chickens and pigs and the consumption of avoparcin in animals in Denmark during 1994–2005.

From 1992 to 2008, antibiotic consumption per kilogram of pig produced fell by more than 50% in Denmark. This change was associated with the implementation of policies to discontinue the use of antimicrobials as AGPs. During the same period, overall pig productivity improved markedly, which suggests that the change in antibiotic consumption did not harm long-term pig productivity *(15)*. The data on broilers and pigs are measured along the left vertical axis; the data on avoparcin are measured along the right vertical axis. Box 2 discusses the effect of withdrawing avoparcin as an AGP.

Fig. 2. Trends in glycopeptide resistance, Denmark, 1994–2005



Note. The data on broilers and pigs are measured along the left vertical axis; the data on avoparcin are measured along the right vertical axis.
Source: Hammerum et al. *(16)*.

Box 2. The effect of withdrawing avoparcin as an AGP in food animals

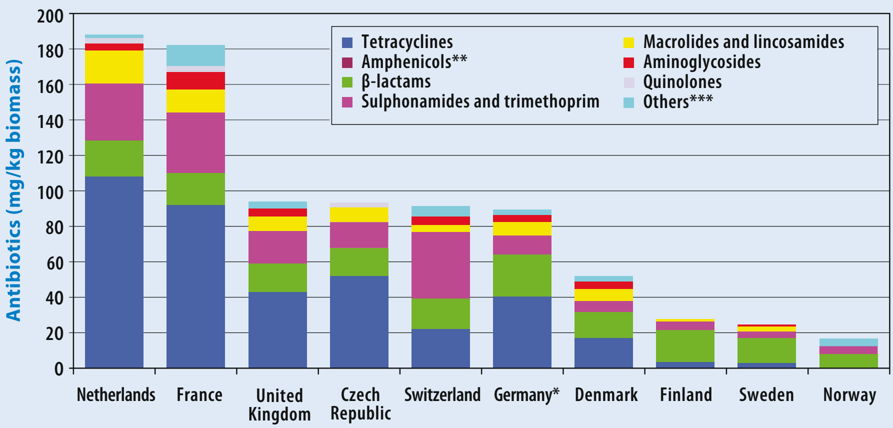
Avoparcin is a glycopeptide antibiotic similar to vancomycin, an antibiotic of last resort in human medicine. Use of avoparcin as an AGP in food animals in Europe resulted in the development and amplification of vancomycin-resistant enterococci in the commensal flora of food animals and on meat from these animals. Also, vancomycin-resistant enterococci in the commensal flora of healthy people increased, despite very limited use of vancomycin in hospitals. This was due to cross-resistance between avoparcin and vancomycin and the transfer of vancomycin-resistant enterococci from food derived from avoparcin-exposed animals. These findings resulted in the withdrawal of avoparcin in the EU in 1997. Data have shown that this intervention resulted in reduction of vancomycin-resistant enterococci in food animals and the general population *(16–18)*.

The main lesson learned is that the use of AGPs can be discontinued and the risk to human health reduced, without harm to animal health or the production economy. Countries should aim to reduce the need for antibiotics in animal husbandry by improving animal health through biosecurity measures, disease prevention, and good hygiene and management practices. Antibiotics should only be used when needed for treatment and then in therapeutic doses (see Chapter 2).

Knowledge of antibiotic use in food animals

At present, most countries have no system for surveillance of antibiotic use, and different methodologies are used to collate and present the available data. For this reason, reliable data are lacking in most countries, and the available data are usually not comparable between countries. Improved surveillance of antibiotic use is urgently needed (see Chapter 2). In the EU, the European Medicines Agency (EMA) works for the development of a harmonized approach to surveillance of antibiotic usage in animals and the collection of data from EU Member States. Fig. 3 shows the usage of veterinary antibiotics in 2007 for 10 European countries, adjusted for the animal biomass at risk of having been treated; the figure representing the total population, in terms of which statistical values are expressed, was not adjusted for the biomass of animals transported to other countries for slaughter.

Fig. 3. Amounts of veterinary antibiotics sold in 2007 per kg biomass of pig meat, poultry meat and cattle meat produced, plus estimated live weight of dairy cattle



* 2005 data.
** Amounts are so small as to be invisible in this figure.
*** The substances included in this category vary between countries.
Source: Grave, Torren-Edo & Mackay *(19)*.

While individual treatment is the rule in human medicine, food animals, such as pigs and broiler chickens, are frequently subjected to herd treatment with antibiotics. Consequently, the frequency of exposure to antibiotics is usually much higher in such animals than in people. This is especially true in countries where AGPs are used, because a large proportion of their animal populations are exposed to antibiotics during most of their lifespan. In these countries, available data therefore suggest that antibiotic usage is higher in food animals than in people. In Denmark, Finland, Norway and Sweden – which have strong policies to restrict antibiotic use and a long tradition of disease prevention in animals – the veterinary usage of antibiotics is relatively low. This shows that antibiotic usage in food-animal production can be limited when a prudent-use policy is implemented (Fig. 3).

Animal feed can contain antibiotics

Antibiotic resistance as a food safety problem

Food products of animal origin are often contaminated with bacteria, and thus likely to constitute the main route of transmitting resistant bacteria and resistance genes from food animals to people. Direct contact with animals or the animal environment, however, may also be of significance, depending on the type of bacteria. Such foods as fruits and vegetables contaminated by animal waste or contaminated water may also constitute a transmission route. Thus, antibiotic resistance is a food safety challenge.

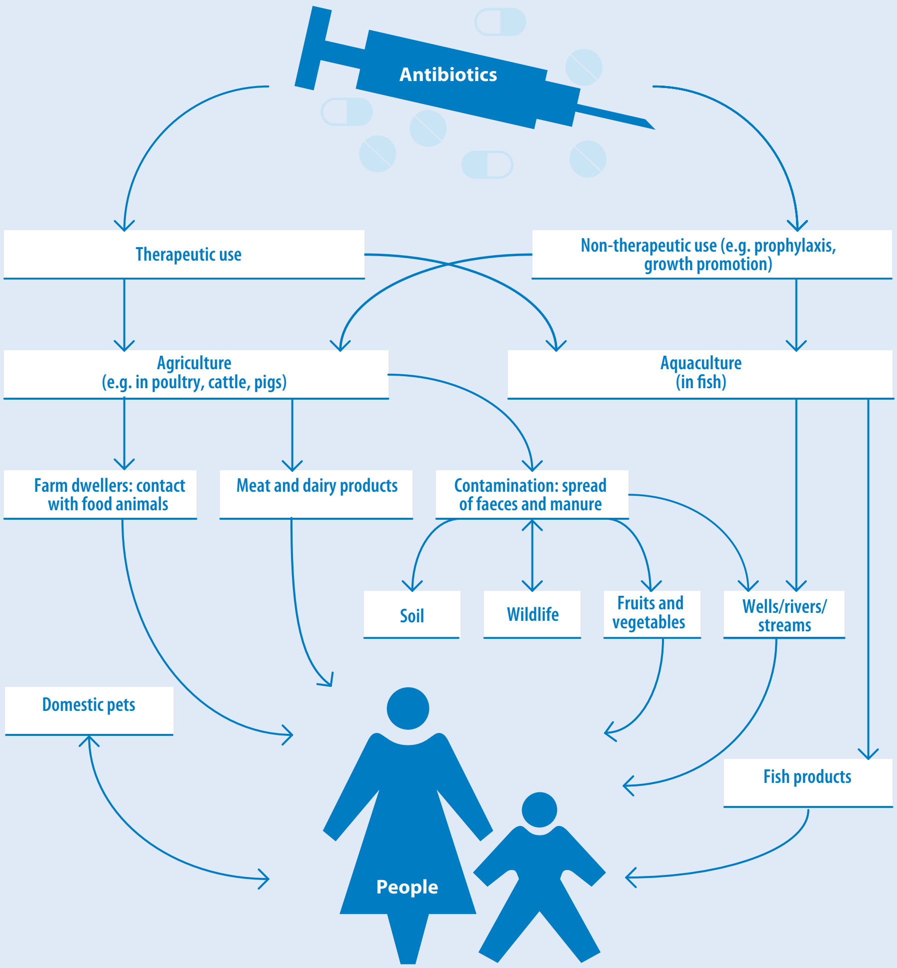
Fig. 4 depicts some of the epidemiological settings in which antibiotics are used and between which bacteria spread. It also highlights the global connectedness of people, animals and animal products through direct contact, travel and trade.

Zoonotic foodborne bacteria, such as *Salmonella* and *Campylobacter*, can contaminate food at some stage of the food-chain. These bacteria typically originate from food animals, so-called healthy carriers. Antibiotic use in the life-cycle of food animals makes it more likely that *Salmonella* and *Campylobacter*

Foods that can contain antibiotic-resistant bacteria

harboured by the animals will be resistant to common antibiotics. For example, the use of enrofloxacin, a fluoroquinolone, in food animals has resulted in the development of resistance in *Salmonella* and *Campylobacter* to ciprofloxacin, a fluoroquinolone used to treat people. Such resistant bacteria have subsequently caused infections in people *(20–23)*. Similarly, resistant *E. coli* can spread from animals to people through the food-chain *(24)*.

Fig. 4. The flow of antiobiotic-resistant bacteria



Source: adapted from an unpublished figure by the Alliance for the Prudent Use of Antibiotics.

An indirect hazard arises when resistance genes (horizontal gene transfer, see the Introduction) move from a resistant bacterium, such as *E. coli* or *Enterococcus* species, in animals to a bacterium pathogenic to people. Resistance genes can readily be transferred between bacteria from terrestrial animals, fish and people; further, such transfers can take place in various environments, such as kitchens, barns and water sources *(25)*.

WHO has developed a list of critically important antibiotics for human medicine (see Annex 1). The prioritized antibiotics, for which comprehensive risk management strategies are needed most urgently, are fluoroquinolones, third- and/or fourth-generation cephalosporins and macrolides.

Antibiotic resistance in Salmonella *species*

Salmonella is a zoonotic agent that can readily infect people. The two most important serovars of *Salmonella* found in animals and their products that cause most human infections are *Salmonella* Enteritidis and *S.* Typhimurium. In general, treatment with antibiotics is not recommended for cases of salmonellosis in otherwise healthy individuals, unless they have a severe disease, such as blood infection. In elderly, very young or immunocompromised patients, however, treatment with an effective antibiotic can save lives. In children and pregnant women who need antibiotic treatment, options are much more limited, because some antibiotics (such as fluoroquinolones) can be toxic and are contraindicated.

Food, primarily of animal origin, is an important reservoir of antibiotic-resistant *Salmonella* that can spread from food animals to people. Foodborne disease in people caused by antibiotic-resistant *Salmonella* is well documented. The foods implicated in these infections are typically beef, pork, poultry and dairy products, but eggs and fresh produce are also culprits. The resistance patterns in *Salmonella* in animals often reflect the selective pressure caused by antibiotic usage in animals. Moreover, EU data show that the occurrence of resistance in *Salmonella* from pigs, cattle and broiler chickens largely resembles the occurrence of resistance reported for *Salmonella* in corresponding foodstuffs and in people *(26)*.

For foodborne *Salmonella*, the resistances of most concern are those against quinolones and cephalosporins, both on the WHO list of critically important antibiotics for human medicine (see Annex 1). Further, multiresistance (resistance to more than four antibiotic classes) is widespread in several *Salmonella* serovars and particularly *S.* Typhimurium, both worldwide and in the European Region *(21)*.

Quinolone resistance

Resistance to quinolones in *Salmonella* from food animals and their products has increased substantially in many countries around the world over the last few years. In the EU, there is considerable variance among the countries, the serovars and the different animal species (resistance is especially high in poultry) and their products *(26)*. The rise in quinolone resistance in animal *Salmonella* isolates has been partly linked to a subsequent increase in human infections with resistant *Salmonella* species; in particular, this is associated with the consumption of contaminated eggs and egg products *(27)*.

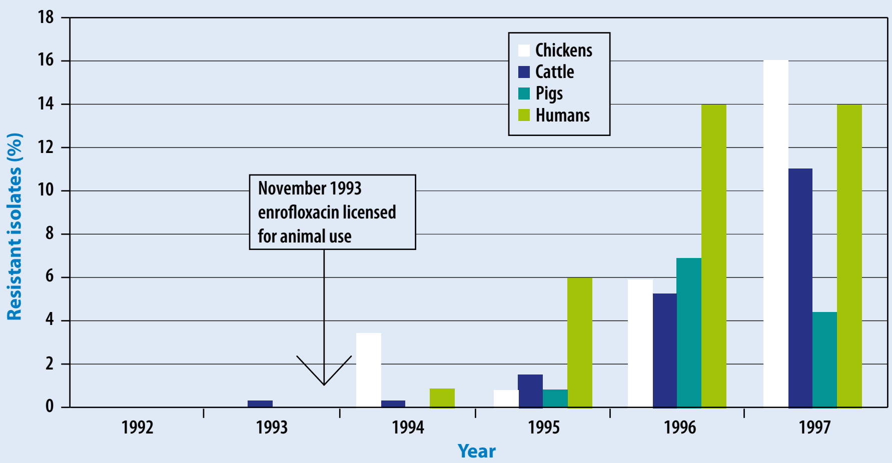
Cephalosporin resistance

In the EU, the prevalence of resistance to third-generation cephalosporins in *Salmonella* from animals and people is low at present. Nevertheless, concerns are rising about the emergence and spread in the EU of *Salmonella* strains that harbour transferable resistance to expanded-spectrum cephalosporins, especially those that produce extended-spectrum β-lactamases (ESBLs – enzymes). A further concern is the increasing emergence of strains of *Salmonella* of animal origin that contain transferable AmpC-like β-lactamases that also inactivate extended-spectrum cephalosporins. In the EU, human infections with cephalosporin-resistant *Salmonella* have usually been related to foreign travel. Nevertheless, their prevalence in people, animals and foods, and reports of links between epidemiological groups show that transfer of resistance along the food-chain is becoming increasingly common *(21)*.

Multiresistant *S.* Typhimurium-like organisms

Since the early 1960s, several multiple-antibiotic-resistant clones of *S.* Typhimurium have emerged. These are typically resistant to a wide range of antibiotics, including some of those listed as critically important antibiotics for human medicine. Such clones – which include such definitive phage types (DTs) as 29, 204, 193 and 104 – have become widely disseminated in both food production animals and people (Fig. 5).

Fig. 5. Quinolone-resistant multiresistant *S.* Typhimurium DT104, United Kingdom, 1992–1997



Source: European Centre for Disease Prevention and Control et al. *(21)*.

Since the late 1990s, reports have increased of the emergence of a variety of so-called monophasic *S.* Typhimurium in many different countries worldwide.[3] These new strains have spread rapidly in certain animal populations and caused numerous human infections in EU Member States, with a death reported in at least one outbreak. In EU countries, two major clonal lines have emerged over the last two decades. Because not all laboratories fully serotype all isolates of putative *S.* Typhimurium, their true incidence in the human population is

[3] This includes *Salmonella* strains with antigenic structures similar to that of *S.* Typhimurium but, in contrast to earlier *S.* Typhimurium-like organism, lacking certain flagella antigens.

unknown. The organisms seem to be associated with pigs and pig products, although their transmission to other food animals is a possibility; these organisms have also been isolated from cattle and poultry in some EU countries *(28)*. Box 3 discusses the human health consequences of antibiotic resistance in *Salmonella.*

Box 3. Consequences for human health of antibiotic resistance in *Salmonella*

Antibiotic resistance in *Salmonella* has been associated with higher frequency and duration of hospital stays, longer illness, a higher risk of invasive infection and a twofold increase in the risk of death in the two years after infection. Compared with infections susceptible to antibiotics, infections with antibiotic-resistant *S.* Typhimurium are associated with an increased risk of invasive disease and death. Also, several studies have shown that patients infected with multidrug-resistant *S.* Typhimurium DT104 may have worse outcomes. Treatment failures, increased hospitalization and higher risk of death have been reported for multiresistant *S.* Typhimurium DT104 that exhibits quinolone resistance *(21).*

Antibiotic resistance in Campylobacter *species*

In the EU, campylobacteriosis is the most commonly reported zoonosis. It is acquired mostly through ingestion of contaminated poultry meat. Campylobacteriosis often results in diarrhoea, which can be associated with bloody stools, fever and severe abdominal pain. The occurrence of campylobacteriosis in parts of the WHO European Region outside the EU is less known, but most likely resembles that in the EU. Most cases are self-limited and do not require antibiotic therapy. When therapy is required, macrolides are commonly used as the first-line drugs, although fluoroquinolones are also widely used. If *Campylobacter* is resistant to these first-line antibiotics, the choice of antibiotic is limited, and treatment failure, combined with greater duration and severity of illness, can occur. Mortality from campylobacteriosis is usually quite low, but it tends to be higher in patients with comorbidities and those infected with antibiotic-resistant strains *(20).*

Campylobacter easily acquires resistance to antibiotics. *Campylobacter* from poultry meat is frequently resistant, including to fluoroquinolones in many countries *(26).* Human infections caused by antibiotic-resistant *Campylobacter* are a growing public health problem.

Quinolone resistance

Several studies have shown a time-limited association between the introduction of fluoroquinolone use in animal production and the emergence and rise of quinolone resistance in both human and animal isolates of *Campylobacter* species. High to very high levels of ciprofloxacin resistance have been reported for isolates from broiler chickens and their meat, pigs and cattle, indicating that these species may serve as reservoirs of resistant *Campylobacter* *(20,21,23,26).*

The adverse health and economic effects of infection with quinolone-resistant *Campylobacter* are of concern because, when compared with infections caused by susceptible strains, these infections have reportedly been associated with longer duration of illness, greater risk of invasive disease and increased frequency of adverse events, including death *(20,29).*

Increasing resistance to fluoroquinolones in *Campylobacter* from people is associated with the use of this class of drugs in food animals. In countries where fluoroquinolones are banned or used sparingly in food animals (such as Australia, Denmark and Norway), studies show low rates of fluoroquinolone resistance in *Campylobacter*, despite their use in human medicine for over 20 years. In countries where fluoroquinolones are or were frequently used in food animals (such as China, Spain and the United States), higher occurrence of resistance is seen in *Campylobacter* from both food animals and people *(20,21,23,30).* Box 4 discusses the withdrawal of fluoroquinolones from use in poultry in the United States.

Box 4. Withdrawal of fluoroquinolone use in poultry in the United States

Campylobacter species cause an estimated 845 024 infections, 8463 hospital admissions and 76 deaths each year in the United States *(31)*. Fluoroquinolones (such as ciprofloxacin) are commonly used in adults with campylobacteriosis and other infections. Fluoroquinolones (such as enrofloxacin) are also used in veterinary medicine. Human infections with fluoroquinolone-resistant *Campylobacter* species have become increasingly common and are associated with consumption of poultry. These findings, along with other data, prompted the United States Food and Drug Administration to propose the withdrawal of enrofloxacin use in poultry in 2000. A lengthy legal hearing concluded with a withdrawal order effective in September 2005. Although clinicians are likely to continue to encounter patients with fluoroquinolone-resistant *Campylobacter* infection and other enteric infections because of the continued circulation of fluoroquinolone-resistant *Campylobacter* species in poultry flocks and people who have acquired a fluoroquinolone-resistant enteric infection during foreign travel, this measure is expected to help reduce the burden of disease due to fluoroquinolone-resistant *Campylobacter* in the United States *(32)*.

Macrolide resistance

So far, resistance to erythromycin in *Campylobacter jejuni* has been below 15% in the EU, both in human and poultry isolates. In general, *C. jejuni* is an organism associated with poultry, whereas *Campylobacter coli* is associated with pigs. In *C. coli*, levels of resistance to erythromycin have been higher than those in *C. jejuni*. The highest rates of resistance have been reported for *C. coli* from pigs, with up to 20% of isolates found to be resistant to erythromycin in 2006 and 2008 in several countries. Levels of resistance above 70% have been recorded in at least one country. The finding that most erythromycin-resistant isolates have been recovered from pigs may reflect prevalent antibiotic choices by veterinary practitioners *(26).*

Resistance to macrolides causes delays and failures in treatment, and the need for alternative antibiotics. Moreover, compared with susceptible infections, infections with macrolide-resistant *Campylobacter* in people are associated with an increased frequency of invasive illness and death *(21,29).*

Antibiotic resistance in E. coli

E. coli strains from animal and water sources that contaminate food can harbour resistance genes that may be transferred to human-adapted bacteria or pathogens during passage through the intestine. If a resistant *E. coli* emerges in a human being and causes disease or transfers its resistance genes to pathogenic bacteria, treatment failure linked to prolonged duration of illness and increased severity will occur.

A current urgent concern is the rapid emergence of so-called ESBL-producing *E. coli* strains that exhibit transferable resistance to third- and fourth-generation expanded-spectrum cephalosporins, particularly as such bacteria often exhibit resistance to other first-line antibiotics, such as fluoroquinolones. ESBLs are capable of breaking down β-lactam antibiotics and thus rendering them ineffective. This includes penicillins and cephalosporins, which are commonly used in hospitals and health clinics as front-line treatments. During the last decade, ESBL-producing *E. coli* strains have emerged both throughout Europe and worldwide, with many infections in hospitals and the community often resulting in deaths in vulnerable individuals *(33)*.

The increase in ESBL-producing *E. coli* strains in recent years has been observed in human infections and among bacteria isolated from food animals, such as cattle and poultry, and particularly broiler chickens. This suggests that food, particularly chicken meat in retail markets, and the environment could be important sources that contribute to the rise of these resistant bacteria *(34)*.

2. Tackling antibiotic resistance in relation to food safety

Addressing antibiotic resistance requires international and intersectoral cooperation, collaboration and communication, since this problem crosses borders and sectors. In addition, international activities are required to guide and support the work needed at the national level. Given the complex nature of antibiotic resistance, the food safety aspects ought to be addressed as an integral part of the response to the challenge.

At both the national and international levels, addressing antibiotic resistance holistically, with interdisciplinary and intersectoral collaboration, is of critical importance. A country can best achieve this by establishing an intersectoral national strategy and action plan that promotes the prudent use of antibiotics in all sectors. This approach would include food safety, and be supported by an intergovernmental steering committee. This calls for establishing a formal mechanism of interaction between the health ministry and other relevant ministries and authorities to address antibiotic resistance in the food-chain.

The rest of this chapter describes in more detail important aspects and areas that countries could consider when addressing antibiotic resistance from a food safety perspective.

Regulatory framework for antibiotic use in food animals

To strike the appropriate balance between the benefits and risks of using antibiotics, a strong regulatory environment is needed at the national and international levels. A comprehensive regulatory framework – supported by standards, guidelines and recommendations – is required to define and control antibiotic use in animals. The regulatory authorities' responsibilities are described in guidelines issued by international bodies, such as those of the Codex Alimentarius Commission and OIE (see Annex 2), and authorities in the European Region, such as the EU. The EU legislation in place is under review, and issues related to antibiotic use are included.

Marketing authorization

Authorization should be required before any veterinary medicinal product can be marketed and used. National regulatory authorities can play a significant role in setting up the requirements for marketing authorization, deciding whether to grant it and specifying the condition of use to support the prudent use of antibiotics in food animals.

In the European Region, the EU has regulatory requirements in place; the principles underlying them – given here as an example – are also applicable to other WHO Member States. In the EU, any veterinary medicinal product must be authorized in accordance with Directive 2001/82/EC, as amended by Directive 2004/28/EC *(35,36)*. Annex I of Directive 2001/82/EC provides detailed descriptions of the data specifying the quality, safety and efficacy of the product that need to be provided when submitting an application for a marketing authorization.

For antibiotics, three specific points need to be addressed:

- risk of antibiotic resistance
- setting of maximum residue limits and withdrawal periods
- generation of preclinical data to establish an appropriate dosage regimen.

First, as the risk of transfer of resistant bacteria or resistance genes from foodstuffs of animal origin to people has been identified as a major safety concern, this risk must be studied for all antibiotic veterinary medicinal products intended for use in food animals. It is studied in accordance with International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (a trilateral EU–Japan–United States programme) guideline 27 (*Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance*) *(37)*. This guidance outlines the types of studies and data recommended to characterize the potential resistance development as it might occur in a food animal under the product's proposed conditions. This includes information that describes attributes of the antibiotic substance, the antibiotic product, the nature of the resistance and the potential exposure of the gut flora in the target animal species.

The second point to be addressed is establishing maximum residue limits (MRLs) and withdrawal periods. When setting acceptable daily intakes and MRLs for veterinary antibiotics, the safety evaluation is carried out in accordance with international guidelines and should include the determination of microbiological effects, as well as toxicological and pharmacological effects. Withdrawal periods should be established for each veterinary antibiotic.

Third, preclinical data should be generated to establish an appropriate dosage regimen, including duration of the usage necessary to ensure the efficacy of the veterinary antibiotic and limit the development of antibiotic resistance. Guidance is available that describes:

- the approach taken for the pharmacokinetic–pharmacodynamic analysis (determining what the body does to a drug and what the drug does to the body) intended to find the best correlation between clinical cure and bacterial killing; and
- how to conduct the clinical efficacy trials.

Of special importance is to find the *optimal* duration of usage, taking into account the risk of developing antibiotic resistance after long-term exposure and the duration of clinical recovery of the animals under therapy.

Definition of condition of use

Following scientific assessment, the marketing authorization issued allows the use of the product according to the approved conditions defined in the summary of product characteristics. This summary should contain the information necessary to enable the product to be used effectively and safely while minimizing the risk of developing antibiotic resistance.

Rational prescription

The relevant authorities should make sure that all veterinary antibiotics used in food animals are prescribed by a veterinarian. In addition, antibiotics should be administered to the animals by a veterinarian or under the supervision of a veterinarian or other suitably authorized person.

Prescription: an important part of prudent use

Off-label use

Off-label use of antibiotics involves using a product in any manner not specified on the label. This includes use in different species, for a different indication or at a dosage different from that on the label.

In the EU, the exceptional off-label use of authorized medicines is allowed under specified conditions described in Directive 2001/82/EC as amended by Directive 2004/28/EC *(35,36)*. These specified conditions are often called the cascade. Where no veterinary medicinal product is authorized in a Member State for a specific condition, the responsible veterinarian may – on his or her direct personal responsibility and particularly to avoid causing unacceptable suffering – treat an animal with a veterinary medicinal product authorized in a particular Member State for another animal species or for another condition in the same species. If no such product is authorized, a medicinal product authorized for human use in a particular Member State or a veterinary medicinal product authorized in another Member State for use in the same species or in another species for the condition in question or for another condition may be used. If, however, no such product exists, a veterinary medicinal product prepared extemporaneously by a person legally authorized to do so – following a veterinary prescription – may be used. These provisions apply for food animals on a particular holding only. The pharmacologically active substances in the medicinal product must have been assessed according to Regulation (EC) 470/2009 (on the residue limits of pharmacologically active substances in foodstuffs of animal origin) *(38)*, and a veterinarian must specify an appropriate withdrawal period, which shall be at least 7 days for eggs, 7 days for milk, 28 days for meat from poultry and mammals (including fat and offal) and 500 degree-days for fish meat.

Pharmacovigilance

The surveillance of veterinary medicinal products under the EU pharmacovigilance system collects suspected adverse reactions in animals and people that relate to the use of veterinary medicinal products under normal conditions. It also takes account of any available information related to the lack of expected efficacy – which is particularly important in detecting the development of antibiotic resistance – and off-label use. Investigations of the validity of the withdrawal period and of potential environmental problems that arise from the use of the product, which may have an adverse effect on the product's risk–benefit balance, are also considered.

In addition, postmarketing authorization commitments (obligations on holders following authorization) could be requested on a case-by-case basis, especially for new classes of drugs that have never been authorized for veterinary use. Such drugs include substances with new mechanisms of action or those belonging to existing classes of antibiotics, but with an extended or altered spectrum of activity, such as the new generation of cephalosporins.

Risk analysis and its effect on antibiotic use

Regulatory authorities can play an important role in analysing the risk of using antibiotics. In the EU, feed additives that contain antibiotics have been banned from use in food animals: avoparcin (1997); ardacin, bacitracin zinc, virginiamycin, tylosin phosphate and spiramycin (1998); and flavophospholipol, salinomycin sodium, avilamycin and monensin sodium (2006).

Following the establishment of the WHO list of critically important antibiotics for human medicine (see Annex 1), EMA produced reflection papers on fluoroquinolones and cephalosporins. Recommendations have been published, and a series of actions taken. These actions require that the summary of product characteristics reflect the appropriate conditions of use in marketing authorizations.

Reduced need for and prudent use of antibiotics in animal husbandry

Preventing infectious diseases in animals

Antibiotics are probably the most valuable drugs in animal production, and maintaining their beneficial effect is therefore of utmost importance. This is supported by prudent use (as described below). Focus should be given to the continuous implementation of appropriate measures for disease prevention, to decrease the need for antibiotics. To minimize infection in food-animal production and decrease the volume of antibiotics used, efforts should aim to improve animal health, thereby eliminating or reducing the need for antibiotics for treatment or prophylaxis. This can be achieved by improving hygiene, biosecurity and health management on farms and preventing disease through the use of vaccines and other measures such as probiotics (beneficial bacteria found in various foods), prebiotics (non-digestible foods that help probiotic bacteria grow and flourish) or competitive exclusion products (intestinal bacterial flora that limit the colonization of some bacterial pathogens).

In aquaculture – for instance, in Norwegian salmon production – the introduction of effective vaccines and improvement of the environmental conditions have been shown to significantly reduce the need for and thus the use of antibiotics. Fig. 6 shows how the introduction of effective medicines in

Ensuring animal health through disease prevention reduces the need for antibiotics

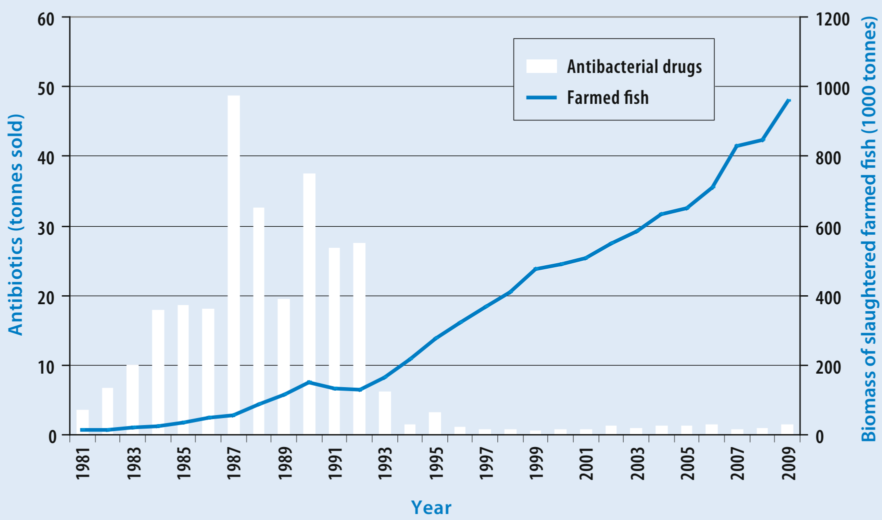
Norwegian aquaculture in 1987 and 1990–1992, in parallel with improved fish-farm management, resulted in a significant reduction in antibiotic use, while production continued to increase. This lesson on the importance of preventive medicine is relevant to all food-animal production.

With the intelligent use of the panoramic range of disease prevention measures, a good health situation and improved economy of animal production can be achieved without the use of antibiotics, unless needed to treat sick animals. This can minimize the risk of spreading antibiotic resistance to human beings.

Ensuring prudent use of antibiotics in animal husbandry

As animals far outnumber people worldwide, the misuse of antibiotics in food-animal production has a broad adverse effect on environmental bacterial flora. Such misuse enhances the risk of developing antibiotic resistance and the associated risks for animal and public health. Ensuring the prudent use of antibiotics in animals is therefore of utmost importance.

Fig. 6. Sales of antibiotics for therapeutic use in farmed fish in Norway versus produced biomass



Source: Markestad & Grave *(39).*

WHO defines appropriate use as "the cost-effective use of antimicrobials which maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of antimicrobial resistance" *(5).* In the context of food-animal production, prudent use means eliminating non-therapeutic uses, including for growth promotion and as feed additives. Another definition of prudent antibiotic use is: the right drug for the right condition for the right amount of time.

A strong national policy for prudent antibiotic use is a necessary first step to minimize misuse of antibiotics in food animals and to reduce problems related to the occurrence of antibiotic resistance in the food-chain. Responsible and prudent use of antibiotics is an essential element in the fight against antibiotic resistance. As described below (see the section on surveillance), a national policy should also require surveillance of antibiotic use and resistance. It should also be part of a national public health policy. Moreover, associated guidelines, surveillance and regulations for compliance should be instituted to protect public health. Further, specific antibiotic use guidelines need to be established for each major type of food animal, with indications for first, second and last-resort choices of antibiotics for treating different bacterial infections.

International interaction is important. All parties must recognize that resistance caused by practices for using antibiotics in food animals in one country travels very quickly to other countries through food exports.

Surveillance of antibiotic use should cover the most important food animals

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The WHO Global Strategy for Containment of Antimicrobial Resistance *(5)* includes six priority recommendations for interventions to reduce the overuse and misuse of antibiotics in food animals for the protection of human health, based on the WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food *(6)*.

1. Require obligatory prescriptions for all antibiotics used for disease control in food animals.
2. In the absence of a public health safety evaluation, terminate or rapidly phase out the use of antibiotics for growth promotion if they are also used for treatment of humans.
3. Create national systems to monitor antibiotic usage in food animals.
4. Introduce pre-licensing safety evaluation of antibiotics [intended for use in food animals] with consideration of potential resistance to human drugs.
5. Monitor resistance to identify emerging health problems and take timely corrective actions to protect human health.
6. Develop guidelines for veterinarians to reduce overuse and misuse of antibiotics in food animals *(5)*.

In addition, the Codex Alimentarius Commission and OIE have developed guidelines on prudent use (see Annex 2), and individual countries and nongovernmental organizations, such as the Alliance for the Prudent Use of Antibiotics, have worked out recommendations and policies *(40,41)*.

Antibiotic resistance is also an ecological problem. Thus, the management of antibiotic resistance may also require tackling the persistence of resistant microorganisms in the environment, including water and soil.

Main principles of responsible and prudent use of antibiotics in food animals

The responsible and prudent use of antibiotics in food animals is intended to minimize potential harm to human health – particularly the development of antibiotic resistance – while ensuring the safe and effective use of antibiotics in veterinary medicine. The main principles of responsible and prudent use of veterinary antibiotics in food animals include the following.

- The need for antibiotics in food animals should be reduced by improving animal health through biosecurity measures (to prevent the introduction of harmful bacteria and the development of infections), disease prevention (including the introduction of effective vaccines, prebiotics and probiotics), and good hygiene and management practices.
- Antibiotics should be administered to food animals only when prescribed by a veterinarian.
- Antibiotics should be used only therapeutically, and use should be based on the results of resistance surveillance (microbial cultures and antibiotic susceptibility testing), as well as clinical experience.
- Use of antibiotics as growth promoters should be eliminated.
- Narrow-spectrum antibiotics should be the first choice when antibiotic therapy is justified.
- Antibiotics identified as critically important for human medicine – particularly fluoroquinolones and third- and fourth-generation cephalosporins – should only be used in animals if their use is justified.
- The use of antibiotics in food animals should be limited to their approved and intended uses, take into consideration on-farm sampling and testing of isolates from food animals during their production, where appropriate, and include adjustments to treatment when problems become evident.
- International guidelines on prudent use of antibiotics, adapted to countries' circumstances, should be followed at the national level. Veterinarians' professional societies should establish guidelines on the appropriate usage of antibiotics for different classes of food animals, including indications of first, second and last-resort choices for treating different bacterial infections.
- Economic incentives that facilitate the inappropriate prescription of antibiotics should be eliminated.

Annex 2 provides information on the relevant international standards and guidelines.

Surveillance

The surveillance of antibiotic resistance in zoonotic and commensal bacteria in different food animal reservoirs and meat products derived from these animals is a prerequisite for understanding the development and dissemination of antibiotic resistance, providing relevant risk assessment data, and implementing and evaluating targeted interventions. This surveillance entails specific and continuous data collection, analysis and reporting that quantitatively monitor temporal trends in the occurrence and distribution of resistance to antibiotics; it also allows the identification of emerging or specific patterns (such as *S.* Typhimurium DT104) of resistance.

Data on the usage of antibiotics in food animals are essential for identifying and quantifying the risk of developing and spreading antibiotic resistance in the food-chain. They are important for assessing the association between usage and the occurrence of resistance in food animals, food and people. Collection of antibiotic usage data supports planning and implementation of evidence-based public health policies and strategies, and provides data for interventions and their evaluation.

Surveillance for antibiotic resistance

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The establishment of national surveillance programmes – on antibiotic usage in food animals and antibiotic resistance in bacteria from food animals and food derived from them – is therefore recognized to be vital to obtaining data for developing national and international policies to contain antibiotic resistance. This is reflected in recommendations given by expert consultations organized by WHO on its own or with FAO and OIE.

Results from a 2007 survey by the WHO Regional Office for Europe show that efforts are needed to better address antibiotic resistance from a food safety perspective. Surveillance is an important component in the prevention and control of antibiotic resistance. The Regional Office survey investigated surveillance of antibiotic usage in food animals and antibiotic resistance in relation to food safety across the Region: 72% of Member States responded. The results indicate that efforts are needed from national public health and veterinary/food safety authorities to ensure the implementation of proper risk-management actions for containment of antibiotic resistance. Only 50% of the responding countries had a system for surveillance of antibiotic resistance in bacteria from food animals, and only 39% surveyed antibiotic usage in food animals. Veterinary prescription for use of antibiotics in food animals was not required in at least five countries, and unknown in several others.

Integrated surveillance and analysis of antibiotic resistance

Antibiotic resistance exists in bacteria in different and potentially linked and/or overlapping reservoirs, including farm animals, food and people. An integrated laboratory-based surveillance programme monitors resistance in all relevant reservoirs, in an attempt to elucidate the sources of resistance and make inferences about the routes of transmission between reservoirs.

In establishing a surveillance programme, several factors must be considered, including: the bacterial species to be included, sampling strategies, isolation procedures, susceptibility testing methods and which antibiotics to test, and data recording, computing and reporting. Quality assurance is an integral part of resistance surveillance.

Surveillance data are gathered not only to elucidate the current situation but also to enable action. The purpose of integrated surveillance is to guide policy development – which involves multiple sectors, such as food animals, food production, the environment, the community and the health care system – to ensure that control measures are implemented in areas likely to have the greatest effect on the containment of resistance in human medicine.

Data on the occurrence of antibiotic resistance and antibiotic usage should ideally be collected and analysed in combination, to provide the basis for effective interventions to control antibiotic resistance.

Surveillance of antibiotic resistance in bacteria of human origin

Antibiotic resistance in bacteria from people can to some extent, and for specific bacterial pathogens, reflect the occurrence of resistance in bacteria in animals and in foods of animal origin. The European Centre for Disease Prevention and Control (ECDC) carries out surveillance of antibiotic resistance in bacteria with relevance to the food safety aspect of public health. It does so through two EU-wide surveillance networks: the European Antimicrobial Resistance Surveillance Network and the European Food- and Waterborne Diseases and Zoonoses Network.

The European Antimicrobial Resistance Surveillance Network collects data on antibiotic resistance in seven invasive pathogens of public health importance: *Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium, E. coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Surveillance is based on national networks that systematically collect data from clinical laboratories in their own countries and report data to a central database at ECDC.

The country experts in the European Food- and Waterborne Diseases and Zoonoses Network submit data on antibiotic resistance in *Salmonella*, *Campylobacter* and verocytotoxin-producing *E. coli* strains to the European Surveillance System (TESSy) at ECDC. To ascertain the quality of data, ECDC has held regular exercises for external quality assessment of the laboratories in the Network.

Surveillance of antibiotic resistance in bacteria from food and food animals

Surveillance of antibiotic resistance in animals and food should cover the zoonotic bacteria *Salmonella* and *Campylobacter*, as well as indicator organisms of the commensal flora, and should supplement surveillance in bacteria of human origin. *E. coli*, *E. faecium* and *E. faecalis* can be used as indicators of the Gram-negative and Gram-positive commensal gut flora, respectively. These three bacteria are commonly isolated from animal faeces, and most resistance phenotypes present in the animal populations are present in these species. Also, the effects of patterns of antibiotic use in a given country and animal species, as well as trends in the occurrence of resistance, can be studied more accurately in indicator bacteria than in pathogens, because all food animals generally carry these indicator bacteria.

Antibiotics to be included in surveillance systems should consist of a concise and feasible set selected for their relevance to human therapeutic use and/or epidemiology. The occurrence of resistance is defined as the proportion of bacteria isolates that are tested for a given antibiotic and found to be resistant. The threshold to be used to categorize bacteria isolates as resistant should be epidemiological cut-off values.[4] Isolates tested for susceptibility should ideally be derived from active surveillance programmes, which enables the determination of bacterial prevalence in the animal populations studied. The greatest benefit may result from focusing on animal populations and food categories that the consumer will most likely be exposed to through food products derived from such animal populations. In general, similar specifications – notably on antibiotics, cut-off values and sampling schemes – can be used for the collection, testing and interpretation of antibiotic susceptibilities of bacteria isolated from animals and food.

Randomized sampling strategies should be preferred, allowing for proper statistical data analysis and reducing the effect of sampling bias. It is particularly important that the bacteria isolates originate from healthy animals sampled from randomly selected holdings or flocks, or randomly selected animals in slaughterhouses. A random sample in each animal population and/or food category targeted will ensure that the entire population is represented and reflect the variability in managerial and hygienic practices in holdings and/or food production facilities and different regions in a country. An approximately equal distribution of samples collected over a year enables the different seasons to be covered.

The sample size – the number of isolates to be tested for susceptibility – should allow, within a predetermined accuracy, the calculation of the proportion of resistance to a particular antibiotic and the detection of changes in this proportion over time. An adequate target number of isolates to be tested for susceptibility per study animal population, per country and per year is a minimum of 170. The number of samples to be collected from each animal population to achieve a minimum of 170 isolates depends on the prevalence of the bacteria species monitored. When prevalence is very low and a large number of samples must be collected to achieve a sufficient amount of isolates, a passive surveillance scheme can be implemented, using isolates derived from targeted or systematic sampling.

According to EU legislation, EU Member States must have a surveillance system that provides comparable data on the occurrence of antibiotic resistance in zoonotic agents from animals and food. To enable the comparison of the occurrence of resistance between different countries, harmonization of the following is requested: protocols on sampling strategies, method of

[4] Epidemiological cut-off values separate naïve, susceptible wild-type populations from isolates that have developed reduced susceptibility to a given antibiotic agent. These values may differ from breakpoints used for clinical purposes, which are defined against a background of clinically relevant data, including therapeutic indication, clinical response data, dosing schedules, pharmacokinetics and pharmacodynamics. The European Committee on Antibiotic Susceptibility Testing has determined the wild-type distribution and its highest minimum inhibitory concentration for a large number of organisms and from these has derived epidemiological cut-off values.

susceptibility testing, antibiotics to be tested and criteria for categorizing isolates as susceptible or resistant, as well as quality control and reporting. The European Food Safety Authority (EFSA) has prepared detailed specifications on minimum requirements for the harmonized surveillance of antibiotic resistance in food animals, so that comparable data may be obtained across the EU. Guidelines for the surveillance of antibiotic resistance in *Salmonella* and *Campylobacter (42)* and in indicator *E. coli* and *Enterococcus* species *(43)* are available.

Surveillance of antibiotic usage in animals

As a minimum, data on overall national and/or regional usage should be collected on a regular basis and reported as weight of active substance per animal species and possibly production type (such as dairy cattle, veal calves), and antibiotic class (such as tetracyclines, macrolides). Also, the data should be further subdivided into therapeutic and growth promotion use. Moreover, the data should be reported per route of administration, such as oral (including in animal feed or water), injection, intramammary, intrauterine and topical application. It should be possible to identify the use of antibiotics defined by WHO as critically important for human medicine (see Annex 1). Data on overall use could be obtained from the following sources:

- the pharmaceutical industry;
- wholesalers;
- pharmacies, for example, through associations of pharmacists and/or medicinal agencies; and
- tariff declarations, for countries without a pharmaceutical industry or wholesalers.

The data sources selected will depend on the national situation, because different countries might have different distribution systems for antibiotics used in animals.

If collecting detailed data for an entire country is difficult, data could be collected through surveys in a representative area by a statistically robust sampling scheme. Such data could be obtained from the records of:

- veterinary practitioners
- farmers.

These data sources could be used to further develop the surveillance programme, so that it collects and reports the usage data per animal species and production class – for example, weaning pigs and slaughter pigs. The usage data should also be combined with data on animal population size and different kinds of animal food production. Ideally, they should also be combined with data on animal health status – on the occurrence of different infections – thus reflecting the need for using different kinds of antibiotics.

Data should be widely disseminated in a timely fashion, preferably in print and electronically, for example, posted on a web site. A description of the data collection protocol – including the antibiotics considered in the surveillance, data sources used and data coverage – should be published with the data.

Within each country, confidentiality agreements and laws should be reviewed and obstacles to reporting usage data resolved. Where confidentiality needs to be protected in certain countries, however, data may be aggregated into antibiotic classes before publication.

To obtain reliable and standardized data harmonized with data on usage of antibiotics in human medicine, it is suggested to follow the latest version of the data collection guidance of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance *(44)* (see Annex 1) or OIE guidelines (see Annex 2). Box 5 discusses international efforts, from a food safety perspective, to strengthen surveillance of antibiotic resistance.

Advocacy and communication

The main objectives of advocacy and communication on antibiotic resistance at the international and national levels should be to raise awareness of the importance of antibiotics in treating bacterial infections and the public health challenges of antibiotic resistance – including within a food safety perspective – and to prompt action to use them prudently in all sectors.

A participatory approach should be used to develop and implement communication strategies that emphasize the importance and benefits of prudent use principles. These strategies should identify relevant target audiences, such as decision-makers; professionals from the health, veterinary and agricultural sectors; farmers; the media; and the general public. These audiences need trustworthy and evidence-based information to guide their decisions and choices.

A customized approach should be taken to select communication channels and tools appropriate to the objectives to be achieved and the audiences desired. Particular emphasis should be placed on professional (re)training of veterinarians, farmers and producers, to correct strongly held misconceptions about the advantages of using antibiotics extensively, as opposed to implementing preventive medicine. The accuracy and effectiveness of

Box 5. Making data speak: international efforts to strengthen surveillance of antibiotic resistance from a food safety perspective

A project – led by the WHO Collaborating Centre on Antibiotic Resistance in Denmark, in collaboration with partner institutions within the WHO Global Foodborne Infections Network – is constructing a web-based food safety portal. The project intends to integrate data from food safety surveillance programmes (for example, those on zoonoses, antibiotic resistance and antibiotic usage from different countries) with other types of data (such as those on food consumption, animal and food production, demographics and climate). It will use these data to investigate new data relations, patterns and risk factors. It will also track trends, using a user-friendly web interface, to allow easy access, presentation and extraction of data.

The portal is also connected to other existing databases, thus receiving automatic updates – for example, from the country databank of the WHO Global Foodborne Infections Network, which collects global data on *Salmonella* serovar distributions. Initiatives to create a link to WHONET are in the pipeline, to facilitate collection and comparisons with global antibiotic susceptibility data on various bacteria, including foodborne pathogens. All data in the portal will be presented through an interface that allows the users to make intuitive queries.

The portal has the potential to become a reference tool in food safety and foodborne disease surveillance, and will be freely accessible to all Member States. The collaboration with the WHO Global Foodborne Infections Network ensures the global perspective of the portal, which will be strengthened with the gradual addition of new data.

messages to the public could be improved by engaging with the media to secure responsible and accurate reporting.

Training and capacity building

Education strategies that emphasize the importance and benefits of the prudent use of antibiotics should be developed and implemented to provide relevant information about antibiotic resistance to farmers, veterinarians and the public.

There is an urgent need to develop guidelines on prudent use, with multi-disciplinary involvement, to reduce misuse of antibiotics in food animals, giving special consideration to antibiotics categorized as critical for human medicine. Veterinarians and farmers should receive training in following these guidelines and, to improve compliance, need to be audited and to receive feedback.

International and regional organizations and networks should support national capacity-building activities that address the food safety aspects of antibiotic resistance. These should cover regulatory issues, surveillance needs, and advocacy of the prudent use of antibiotics.

Knowledge gaps and research needs

The understanding of antibiotic resistance related to food safety still has many knowledge gaps that research is needed to fill. For example, the available information on the burden of disease from antibiotic-resistant organisms is mainly qualitative; research to quantify the differential burden of disease that results from resistant versus susceptible bacterial strains needs to be promoted. Such information would provide an additional dimension to the magnitude of the issues and support risk assessment and management, including the development of cost-effective strategies to counteract the development and spread of antibiotic resistance.

In many countries, epidemiological data on antibiotic resistance, from a food safety perspective, are scarce. Also, little information is publicly available about antibiotic usage in food-animal production. These are major obstacles to monitoring the effects and effectiveness of policies, particularly those to ban the use of antibiotics as growth promoters and to restrict antibiotic use according to principles of prudent use. Consequently, investment is needed in:

- more and better national data on the occurrence of antibiotic resistance in relevant bacteria from food animals, food products and people; and
- data on the usage of various types of antibiotics in different types of food animals.

As data should be comparable between countries, harmonized approaches for surveillance of antibiotic resistance and usage should be developed and applied, following international standards and recommendations.

Governments and academic networks, working with the private sector, need to continue to play an active role in research on antibiotics and resistance. Surveillance data should be actively used in epidemiological research and risk assessment, including the evaluation of interventions. Also, research that can further improve the understanding of mechanisms of resistance development and transfer should be promoted. Moreover, more research is needed to develop new antibiotics and alternative approaches to antibiotic therapy.

3. Conclusions and action points

Antibiotic resistance related to food safety is an increasing public health problem that urgently needs to be addressed at the national level.

Modern food-animal production uses large amounts of antibiotics not only for therapeutic purposes but also to prevent disease and promote animal growth. As a result, large numbers of healthy animals are routinely or often exposed to antibiotics. This provides favourable conditions for the emergence, development, spread and persistence of antibiotic-resistant bacteria capable of causing infections in animals and people. Resistant zoonotic bacteria carried by food animals can spread to and infect people, usually through food but also through direct contact with animals or environmental spread. The genes that encode antibiotic resistance can also be transferred from commensal bacteria to human pathogens. Because food animals and foods of animal origin are traded worldwide, antibiotic resistance affecting the food supply of one country becomes a potential problem for others.

The rest of this chapter lists suggested action points that national authorities can consider. Implementing most of these could help prevent and contain antibiotic resistance in the food-chain, thereby protecting human health.

Overall coordination

It is suggested that national governments give consideration to establishing:

- an intersectoral national strategy and action plan on antibiotic resistance, including the food safety perspective and supported by an intergovernmental steering committee, which should promote the prudent use of antibiotics in all sectors; and
- a formal mechanism of interaction between the health ministry and other relevant ministries and authorities, to address the issue of antibiotic resistance in the food-chain.

Regulation

It is suggested that the veterinary, agricultural and pharmaceutical authorities at the national level give consideration to:

- establishing a regulatory framework for authorizing and controlling veterinary medicines, including antibiotics;

- introducing a pre-licensing safety evaluation of antibiotics intended for animals, with consideration given to the potential development of resistance to antibiotics used in human medicine;
- eliminating the use of antibiotics as growth promoters;
- requiring that antibiotics be administered to animals only when prescribed by a veterinarian; and
- requiring that antibiotics identified as critically important in human medicine – especially fluoroquinolones and third- and fourth-generation cephalosporins – only be used in food animals if their use is justified.

Reduced need for and prudent use of antibiotics in animal husbandry

Antibiotics are valuable medicines and should be used only therapeutically and as little as possible. It is important that veterinary, agricultural and pharmaceutical authorities at the national level – in collaboration with the private sector – promote preventive veterinary medicine and the prudent use of antibiotics in interaction with all relevant stakeholders, particularly veterinary practitioners and farmers. This would include:

- reducing the need for antibiotics in animal husbandry, by improving animal health through biosecurity measures, disease prevention (including the introduction of effective vaccines), and good hygiene and management practices;
- implementing international guidelines on prudent use of antibiotics in food animals at the national level, adapted to national circumstances;
- establishing guidelines on the prudent and appropriate use of antibiotics for different classes of food animals, including indications of first, second and last-resort choices for treating various bacterial infections, in collaboration with veterinary societies; and
- eliminating economic incentives that facilitate the inappropriate prescription of antibiotics.

Surveillance

It is suggested that public health, veterinary and food authorities give consideration to establishing:

- a surveillance system for usage of antibiotics in people and food animals, to monitor:
  - overall usage in people and animals, divided according to major groups of antibiotics;

  - usage stratified by major groups (species, production type) of food animals;
- an integrated (among public health, food and veterinary sectors) surveillance system for antibiotic resistance in selected foodborne bacteria, to monitor current and emerging resistance patterns and enable timely corrective action to protect human health;
- joint analysis and reporting, in publicly available annual reports, of data on antibiotic resistance and usage, both from the public health and the veterinary and/or food sectors;
- a multidisciplinary task force that involves public health, veterinary and food authorities, to use the surveillance data to identify trends, assess risks and ensure timely implementation of focused interventions; and
- common protocols to facilitate global harmonization in surveillance of antibiotic usage in people and animals and in surveillance of antibiotic resistance.

For the surveillance of resistance, a three-part approach that includes bacteria from human clinical cases, food animals, and animal-derived food products is preferable. When this is not practicable, surveillance can be implemented incrementally, alternated over time or limited to priority study populations. Susceptibility data should be quantitative.

The following suggestions are offered to help prioritize surveillance components.

1. Where resources are limited, the first priority is to monitor human isolates, which may be derived from hospitals, health care facilities and outpatient clinics and which may include representative strains from outbreaks. It is suggested to include all available isolates of:
   - *Salmonella* from blood and stool
   - *Campylobacter* from blood and stool
   - *E. coli* from blood and urinary tract infections.

2. Bacterial contaminants have multiple entry points to sneak into the food-chain. For countries starting surveillance programmes, retail meats are the second priority for monitoring, since these represent the major route of human exposure. Retail meat samples should reflect regional consumption patterns. Suggested bacteria to include are *Salmonella*, *E. coli* and *Campylobacter*.

3. Suggested animal isolates to include in surveillance are *Salmonella*, *E. coli* and *Campylobacter*. If on-farm sampling is not possible, then bacteria from healthy animals at slaughter can be used as a surrogate for resistance estimates in food animals for *Salmonella*, *E. coli*, *Campylobacter* or local priorities.

Advocacy and communication

It is suggested that public health, veterinary and food authorities engage in advocacy and communication activities that raise awareness of the food safety perspective of antibiotic resistance and how to prevent the development and spread of antibiotic resistance in the food-chain, by:

- emphasizing a participatory approach (decision-makers, professionals, producers, media and the general public);
- raising awareness of the food safety perspective of antibiotic resistance and highlighting the prudent use of quality antibiotics; and
- careful and targeted use of media to improve the effectiveness of the messages on antibiotic resistance to the public at large.

Training and capacity building

It is suggested that veterinary, agriculture and food authorities give consideration to:

- developing and implementing educational strategies that emphasize the importance and benefits of prudent use principles, to provide relevant information on antibiotic resistance to producers, stakeholders and the public;
- developing guidelines on prudent use of antibiotics in food animals through multidisciplinary involvement, taking into consideration antimicrobials categorized as critically important for human medicine;
- providing training for both veterinarians and farmers on the application of guidelines on prudent use; and using auditing and feedback to veterinarians and farmers to improve compliance; and
- strengthening capacity-building activities and addressing antibiotic resistance in a food safety perspective.

Knowledge gaps and research needs

It is suggested that public health, veterinary and food authorities – with education and research authorities and the private sector – give consideration to:

- securing comparable national data on the occurrence of antibiotic resistance in relevant bacteria from food animals, food products and people, and on the use of various types of antibiotics in different categories of food animals;

- actively using surveillance data in epidemiological research and risk assessment, including the evaluation of interventions;
- promoting research that can further improve the understanding of mechanisms of resistance development and transfer; and
- strengthening research on the development of new antibiotics and alternative approaches to antibiotic therapy.

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Annex 1. International partnerships on antibiotic resistance from a food safety perspective

WHO activities for global containment of foodborne resistance

Concerned about the extensive use of antibiotics in food-animal production accelerating the development of resistant bacteria in animals and transmitting it to people via the food-chain, the World Health Assembly urged Member States in resolution WHA51.17 to encourage the reduced and rational use of antibiotics in food-animal production *(1)*. This resulted in the further development of WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food *(2)*, with the participation of the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE) and their inclusion in the WHO Global Strategy for Containment of Antimicrobial Resistance *(3)*. The Principles provide a framework of recommendations to protect human health by reducing the overuse and misuse of antimicrobials in food animals. Their overall objective is "to minimize the negative human health impact of the use of antibiotics in food producing animals whilst at the same time providing for their safe and effective use in veterinary medicine" *(4)*.

After publishing the Global Principles *(2)*, WHO followed up by holding more than 10 expert consultations (some held jointly with FAO and OIE):

- to assess the public health risk associated with the usage of antibiotics in animal husbandry (including aquaculture) *(4–6)*; and
- to propose high-level management options to address the risks identified *(2,7,8)*.

This consultative process, involving many of the leading scientists in this area, showed unequivocally that antibiotic usage in food animals can select for antibiotic resistance in bacteria in animals, especially in the gut. Subsequently, these resistant bacteria or their genetic determinants can be transferred to people via the food-chain. Further, the consultative process resulted in the development of the WHO list of critically important antimicrobials for human medicine *(9–12)*.

WHO established the Advisory Group on Integrated Surveillance of Antimicrobial Resistance *(12)* in 2008 to support its effort to minimize the adverse effect on public health of antibiotic resistance associated with antibiotic usage in food animals. In particular, the Advisory Group assists WHO on matters related to the integrated surveillance of antibiotic resistance and the containment of food-related antibiotic resistance. The main objectives of the Advisory Group include promoting harmonization of data and sharing experiences internationally. The Advisory Group's four subcommittees (on surveillance of antibiotic usage and resistance, building capacity and managing data) are developing practical tools, guidelines and protocols to support WHO Member States in implementing national programmes for integrated surveillance of antibiotic resistance and usage.

WHO works closely with partners at the international, regional and national levels to ensure the implementation of the WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food *(2)*. In particular, it works on banning animal growth promoters (AGPs), promoting the rational prescription and use of veterinary antibiotics and the restriction of use in food animals of critically important antimicrobials for human medicine, particularly quinolones and third- and fourth-generation cephalosporins. WHO helps to build capacity in Member States through training courses and sentinel studies, to support the implementation of:

- surveillance of antibiotic usage and resistance;
- risk assessment approaches to support selection of risk management options; and
- intervention strategies to contain antibiotic resistance.

The sharing of data and experience between countries is extremely important and should be based on surveillance systems set up according to WHO and OIE international standards. Documentation on the effect of specific national interventions to prevent antibiotic resistance is increasingly used across borders.

Critically important antimicrobials for human medicine

For many serious infections in people (including enteric infections), few or no alternate antibiotics can be used if antibiotic resistance develops. These antibiotic classes have various names, such as critically important, essential, reserve or last resort.

WHO started its work in this area by organizing an expert consultation in 2005, to develop the list of critically important antimicrobials for human medicine *(9)*. Expert meetings in 2007 and in 2009 produced the updated (second and third) editions of the WHO list *(10,12)*.

To develop the WHO list, all antibiotics used to treat bacterial infections in people were classified into three categories: critically important, highly important and important. Two criteria were used to assign each antibiotic (or class) to a category:

1. sole therapy or one of few alternatives to treat serious human disease; and
2. antibiotic used to treat diseases caused by organisms that may be transmitted via non-human sources or diseases causes by organisms that may acquire resistance genes from non-human sources.

Critically important antibiotics meet both criteria; highly important antibiotics meet either the first or second, and important antibiotics meet neither.

The WHO classification was conceived mainly to guide decisions about risk management strategies for antibiotic use. WHO regularly updates its list of critically important antimicrobial agents as new information becomes available, including data on resistance patterns, new and emerging diseases and the development of new drugs.

WHO prioritized agents categorized as critically important to allow allocation of resources to the classes for which comprehensive risk management strategies are needed most urgently: quinolones, third- and fourth-generation cephalosporins and macrolides. The WHO list should be used to support more comprehensive assessments of risk, which should: include information on the potential development of resistance in pathogens in animals (release assessment) and the potential spread of resistant organisms or their genes from animals to people (exposure assessment); and integrate these data into a comprehensive assessment of risk and strategies to manage it.

FAO work on antibiotic resistance

Given its mandate to lead international efforts to reduce world hunger, FAO plays a critical role in trying to ensure that globalized food production can meet the needs of an increasing global population. This includes promoting food production practices that will result in safe and nutritious food for consumers. While antibiotics can play a critical role in food production, the need to balance their use, to ensure they remain a valuable tool for both human and animal health, is well recognized. Current FAO work emphasizes the usage of antibiotics in animal (including fish) production.

FAO's promotion of good aquaculture practices emphasizes the need to minimize the use of antibiotics and addresses different levels. Raising awareness about the public health effects of using antibiotics in aquaculture is a critical component. This is done through FAO regional workshops on management of fish safety and quality, which have so far focused mainly on Asia and Africa. Also, FAO is implementing various initiatives at the field level, where site-specific good aquaculture practices are being developed, based on analysis of pond conditions and local practices. Tailoring guidance to local conditions aims to make practices more sustainable in the long term.

FAO also works through high-level policy meetings, particularly those of the Committee on Fisheries. At the Committee's 29th session at the end of January 2011, FAO member countries endorsed technical guidelines for aquaculture certification that emphasize minimal and responsible use of antibiotics.

In providing advice and guidance to policy-makers in the aquaculture sector, FAO starts by trying to understand the challenges this sector faces in addressing antibiotic usage. For example, FAO convened the expert Workshop on Improving Biosecurity through Prudent and Responsible Use of Veterinary Medicines in Aquatic Food Production in December 2009. It identified several major sectoral concerns, including:

- authorization of veterinary medicines and related issues;
- the need for technical assistance (for example, environmental and human impact evaluation capacity and trading compliance); and
- harmonization of international standards.

FAO has surveyed the use of veterinary medicines in aquaculture internationally and in several Asian countries, and is preparing to report on it. Such information will be used to support the preparation of the Technical Guidelines on Prudent and Responsible Use of Veterinary Medicines in Aquaculture of the FAO Code of Conduct for Responsible Fisheries.

The use of antibiotics to treat animal diseases benefits animal health and therefore helps support the livelihoods of livestock owners and the economies of developing countries. Using antibiotics to treat and prevent diseases in food animals, however, is also associated with the risk of the emergence and spread of antibiotic-resistant microorganisms. The risk is particularly high in countries with weak or inadequate national policies, regulation, and surveillance and monitoring systems for antibiotic usage, resistance and residues in food.

FAO is implementing a series of interlinked activities in East Africa, to strengthen national and/or regional policies, capacities and systems to regulate and manage the risks of antibiotic resistance. For example, a pilot project in Kenya aims to help alleviate poverty and improve nutrition, household food security and income, while identifying and addressing risk factors to human health and helping to optimize market opportunities.

Central to such projects is the approach of studying the whole food-chain to assess and quantify microbial contamination, to identify and quantify antibiotic-resistant strains and to identify the critical stages at which prevention and control measures can be most effective. The use of locally generated data and information on local practices is critical to guide policy and develop guidelines that address the prudent use of antibiotics in a manner suitable to a particular country or region. Working with international partners in such initiatives, such as WHO and OIE, is important to ensure the application of the integrated approach needed to address antibiotic resistance.

Codex Alimentarius Commission work on antibiotic resistance

The Codex Alimentarius Commission was created in 1963 by FAO and WHO to develop food standards, guidelines and related texts, such as codes of practice, under the Joint FAO/WHO Food Standards Programme. The main purposes of this Programme are to protect consumers' health, ensure fair practices in the food trade and promote coordination of all food-standards work undertaken by international governmental and nongovernmental organizations. Several of the Commission's subsidiary bodies have considered the public health implications of using antibiotics in food animals, including:

- primarily the Committee on Residues of Veterinary Drugs in Foods, Committee on Food Hygiene and ad hoc Intergovernmental Task Force on Animal Feeding; and
- to a lesser extent the Committee on Pesticide Residues and Committee on Fish and Fishery Products.

Approaches to understanding the public health significance of antibiotic resistance within each of these groups have tended to focus on the professional disciplines reflected by the traditional membership of these groups: safety of residues in the Committee on Residues of Veterinary Drugs in Foods, microbiological risk profiles in the Committee on Food Hygiene, and feeding practices and the manufacture of animal feeds in the ad hoc Intergovernmental Task Force on Animal Feeding.

In recognizing the need for a more general and multidisciplinary response to antibiotic issues, in 2006 the Commission established a Codex ad hoc Intergovernmental Task Force on Antimicrobial Resistance, to deal specifically with this subject *(13)*. At its fourth and last session in October 2010, the Task Force completed its work to develop guidelines on risk analysis of antimicrobial resistance *(14)*.

OIE work on antibiotic resistance

OIE is an intergovernmental organization with a mandate from its 178 Member Countries and Territories (OIE Members) to improve animal health, veterinary public health and animal welfare worldwide. The standards, guidelines and recommendations developed by OIE are recognized as the reference documents for animal health and zoonoses by the World Trade Organization (WTO) in the framework of its Agreement on the Application of the Sanitary and Phytosanitary Measures.

Antibiotics are essential for treating and controlling infectious diseases in animals. Animal health has a substantial effect on food safety and food security, both of which substantially affect human health. OIE therefore considers that ensuring continued access to effective antibiotics is important.

Antibiotic resistance is a global human and animal health concern that is influenced by both human and non-human antibiotic usage. The human, animal and plant sectors therefore have a shared responsibility to prevent or minimize antibiotic resistance selection pressures on both human and non-human pathogens.

OIE has worked for more than a decade on veterinary medicinal products, including antibiotics, and developed a coherent strategy for its activities in this area. Considering that antibiotic resistance is a global multidisciplinary issue, OIE works closely with its Members, WHO, FAO and the Codex Alimentarius Commission.

Following the FAO/OIE/WHO workshops on non-human antimicrobial usage and antimicrobial resistance held in 2003 (on scientific assessment) *(4)* and 2004 (on management options) *(7)*, OIE developed a list of antimicrobials of veterinary importance *(15)*, in parallel with the WHO list for human medicine.

OIE promotes the responsible and prudent use of antibiotics in terrestrial and aquatic animals, so as to preserve their therapeutic efficacy and prolong their use in both animals and people. It also pays specific attention to the need to monitor antibiotic resistance. OIE has developed standards and guidelines to provide methodologies for OIE Members to appropriately address the emergence or spread of resistant bacteria that results from the use of antibiotics in food animals and to contain antibiotic resistance by controlling the use of antibiotics (available in the two OIE publications: the Terrestrial Animal Health Code and *Manual of diagnostic tests and vaccines for terrestrial animals* (see Annex 2).

In parallel and in synergy with the development of standards and guidelines, OIE provides continuing support to its veterinary services and laboratories, to enable OIE Members to implement these standards and guidelines.

The OIE Pathway and its Tool for the Evaluation of the Performance of Veterinary Services serve as a guide for OIE Members that seek to ensure that their services comply with international quality standards. Also, OIE continues to develop new tools to provide guidance and a framework to its Members to help them to update their national legislation in accordance with international standards, including marketing approval and control of veterinary products.

The OIE Laboratory Twinning Programme creates opportunities for developing and in-transition countries to develop laboratory diagnostic methods and scientific knowledge based on OIE standards. The Programme aims to mobilize the existing expertise of the whole network of OIE reference laboratories and collaborating centres,[1] to develop capacities in geographic areas that are currently underrepresented.

In this network, OIE and OIE Members can rely on the support and expertise of the collaborating centres on Veterinary Medicinal Products (France) and Diagnosis and Control of Animal Diseases and Related Veterinary Product Assessment in Asia (Japan), and the Reference Laboratory on Antimicrobial Resistance (United Kingdom).

OIE emphasizes the need for harmonized approaches to the approval and use of veterinary medicinal products, recognizing the key role of good governance in all matters related to veterinary medicinal products. As an associated Member founder of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products, OIE actively promotes the need to harmonize the approval and registration process for veterinary medicinal products.

OIE communicates all these activities through publications, international and regional conferences, and regional training workshop for OIE national focal points on veterinary products. These focal points are nominated by the OIE Delegates, and their tasks (conducted for each Member under the authority of its OIE Delegate) include: communication with and establishment of networks of authorities and experts on veterinary products, monitoring of legislation and the control of veterinary products, and consultations and preparation of comments on drafts of proposed OIE standards, guidelines and recommendations related to veterinary products.

1 Lists are available of OIE reference laboratories (http://www.oie.int/our-scientific-expertise/reference-laboratories/list-of-laboratories) and collaborating centres (http://www.oie.int/our-scientific-expertise/collaborating-centres/list-of-centres).

European Union (EU) perspective

In recent years, antibiotic resistance has become one of the priority areas of the European Commission's Directorate-General for Health and Consumer Policy. Its 2009 staff working paper on antibiotic resistance *(16)* compiled the initiatives undertaken so far. Then followed proposals for risk assessment and management, monitoring of antibiotic resistance and use, scientific research and international cooperation. Specific proposals were made on the authorization and use of veterinary antibiotics, particularly critically important ones.

To tackle the issue of antibiotic resistance and related aspects, the Commission has strengthened its internal cooperation among public health, food safety and animal health disciplines. The Commission has announced that it will develop a five-year strategy on antibiotic resistance that covers all these areas and includes concrete proposals for action.

The European Centre for Disease Prevention and Control (ECDC) is an independent EU agency that works in partnership with national health protection bodies across Europe to strengthen and develop continent-wide disease surveillance and early warning systems. ECDC's programme on antibiotic resistance and health-care-associated infections covers issues in both the community and hospitals. Programme activities include surveillance of antibiotic-resistant bacteria, antibiotic consumption and various types of health-care-associated infections, and the provision of scientific advice on their prevention and control, communication and training.

The European Food Safety Authority (EFSA) anchors EU risk assessment of food and feed safety and thereby covers antibiotic resistance, as this has a zoonotic perspective. Continuous and updated information on antibiotic resistance is essential to guide risk profiling, assessment and management and to determine the effects of possible interventions. To provide continuous and updated information on antibiotic resistance, Directive 2003/99/EC on the monitoring of zoonoses and zoonotic agents dictates to EU Member States their obligation to monitor and report on antibiotic resistance in *Salmonella* and *Campylobacter* isolates from animals and food *(17)*. The monitoring and reporting of resistance data from indicator organisms (commensal *Escherichia coli* and *Enterococcus* species) is voluntary. Further, Directive 2003/99/EC foresees that the monitoring of antibiotic resistance is based on the surveillance systems in place in Member States, which may differ in the origin of and laboratory testing of isolates. EFSA collects and examines the data on antibiotic resistance from Member States and presents them in official reports *(18)*.

The European Medicines Agency (EMA) is a decentralized body of the EU. Its main responsibility is to protect and promote public and animal health, through the evaluation and supervision of medicines for human and veterinary use. The Committee for Medicinal Products for Veterinary Use provides scientific recommendations and opinions on veterinary medicines when those are related to antibiotics. The Committee is supported by its Scientific Advisory Group on Antimicrobials *(19–21)*, and considers maintaining the efficacy of antibiotics and minimizing the development of resistance one of the most important tasks in veterinary medicine.

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Annex 2. Relevant international standards and guidelines

The FAO/WHO Codex Alimentarius Commission and OIE have both recognized the importance of antibiotic resistance and the risks to human and animal health associated with the use of antibiotics. They work together to ensure a coordinated and complementary approach to contain antibiotic resistance throughout the entire food-chain, from primary production through to the final consumers.

Arising from their respective mandates, the Commission and OIE have developed standards and guidelines to provide methodologies and guidance to address the emergence or spread of resistant bacteria that result from antibiotic use and to contain antibiotic resistance by controlling this use.

Codex and OIE standards, guidelines and recommendations result from transparent and democratic processes. All of them have been adopted by consensus of their respective members and are regularly updated. To ensure synergy and complementarity, the Commission and the OIE participate in each other's standard setting processes.

The significance of Codex and OIE standards has increased since the creation of the WTO, which, through its Agreement on the Application of Sanitary and Phytosanitary Measures, identifies Codex and OIE texts as the benchmark measures for food safety, and animal health and zoonoses, respectively. WTO members are therefore encouraged to base their national measures on and to harmonize them with Codex and OIE texts.

Codex texts

Specific Codex texts developed on antibiotic resistance include the Code of Practice to Minimize and Contain Antimicrobial Resistance *(1)* and draft guidelines for risk analysis of foodborne antimicrobial resistance *(2)*, which were recently finalized by the Codex *ad hoc* Intergovernmental Task Force on Antimicrobial Resistance *(3)*. In addition, other Codex texts take account of antibiotic resistance, particularly in relation to the use of antibiotics, such as the Code of Practice on Good Animal Feeding *(4)* and Section 6 on aquaculture production in the code of practice for fish and fishery products *(5)*.

Code to minimize and contain antimicrobial resistance

The Code of Practice to Minimize and Contain Antimicrobial Resistance *(1)* provides additional guidance for the responsible and prudent use of antibiotics in food animals and should be read in conjunction with the *Guidelines for the design and implementation of national regulatory food safety assurance programme associated with the use of veterinary drugs in food producing animals (6)*. Its objectives are to minimize the potential adverse effect on public health that results from the use of antibiotics in food animals, particularly the development of antibiotic resistance. It also highlights the importance of providing for the safe and effective use of antibiotics in veterinary medicine by maintaining their efficacy. The document defines the responsibilities of authorities and groups involved in the authorization, production, control, distribution and use of veterinary antibiotics, such as national regulatory authorities, the veterinary pharmaceutical industry, veterinarians, and producers and distributors of food animals.

While focusing on the use of antibiotics in food animals, the Code recognizes that antibiotic resistance is also an ecological problem and that managing it may require addressing the persistence of resistant microorganisms in the environment. The Code includes recommendations intended to prevent or reduce the selection of antibiotic-resistant microorganisms in animals and people:

- to protect consumer health, by ensuring the safety of food of animal origin intended for human consumption;
- to prevent or reduce, as far as possible, the direct and indirect transfer of resistant microorganisms or resistance determinants within animal populations (and from food animals) to people;
- to prevent the contamination of food derived from animals with antimicrobial residues that exceed the established maximum residue limits (MRLs); and
- to comply with the ethical obligation and economic need to maintain animal health.

The Code does not address environmental issues related to antibiotic resistance from the use of veterinary antibiotics, but encourages all those involved to consider the ecological aspects during implementation.

Draft guidelines on risk analysis of antimicrobial resistance

These guidelines *(2,3)* have several aims:

- to provide science-based guidance on processes and methodologies for risk analysis and their application to foodborne antibiotic resistance related to non-human use of antibiotics;
- to assess the risk of antibiotic resistance in microorganisms and resistance determinants to human health associated with their presence in food and animal feed (including aquaculture); and
- to assess the risk of transmission through food and animal feed and to provide advice on appropriate risk management activities to reduce it.

Further, the guidelines will address the risk associated with different sectors' antibiotic use, such as in veterinary applications, plant protection and food processing.

OIE standards and guidelines

The relevant standards and guidelines are published in the Terrestrial Animal Health Code, in four chapters in the section dedicated to veterinary public health *(7)*. These chapters cover:

(a) harmonization of national antimicrobial resistance surveillance and monitoring programmes;
(b) monitoring of the quantities of antimicrobials used in animal husbandry;
(c) responsible and prudent use of antimicrobial agents in veterinary medicine; and
(d) risk assessment for antimicrobial resistance from the use of antimicrobials in animals.

The relevant standards and guidelines are also published in the *Manual of diagnostic tests and vaccines for terrestrial animals (8)*, which contains a chapter on laboratory methodologies for bacterial antibiotic susceptibility testing. These publications, as well as the OIE list of antimicrobials of veterinary importance *(9)*, are being updated, with the participation of WHO and FAO. Further, a new chapter on principles for responsible and prudent use of antibiotics in aquatic animals is under development and will soon be published in the Aquatic Animal Health Code *(10)*.

Relevant EU guidelines

In the EU, the Committee for Medicinal Products for Veterinary Use's revised guideline on the summary product characteristics for antibiotics *(11)* provides practical recommendations on the prudent use of antibiotics in animals. In food animals, the recommendations mainly focus on situations in which the use of antibiotics may have a high potential for selecting antibiotic-resistant bacteria in the food-chain: for example, when treatment is to be given to animal groups or flocks. The guideline specifies that under the authorized conditions for use of the antibiotic, the target bacterial species shall be listed for each target animal species and therapeutic indication.

Recommendations for prudent use of antibiotics should be made to retain therapeutic efficacy and to minimize the spread of resistance.

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The WHO Regional Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

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